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**14. ABSTRACT**

Mild traumatic brain injury (mTBI) is one of the major health problems facing military servicemembers returning from deployments. White matter axonal damage, as measured by neuroimaging techniques like Diffusion Weighted Imaging (DWI), is one of the hypothesized mechanisms contributing to the cognitive and affective sequalae of mTBI. Presently, many of the findings in the literature examining the association between DWI and neuropsychological outcome are contradictory, possibly due to differences in stage of recovery at the time of assessment. This study will address this problem by collecting measures of white matter integrity and concomitant neuropsychological status at five time points in the first year following an mTBI. During the first year, study preparations, including ethical approval, hiring and training of new staff, purchasing of equipment and materials, and validation of neuroimaging protocols, were completed ahead of schedule. During the past year, we have collected usable data from a total of 13 participants. These data have been cleaned and preliminary analyses suggest that we are able to identify meaningful trends in the data, although the sample is still far too small to make valid conclusions.

**15. SUBJECT TERMS**

TBI, traumatic brain injury, concussion, DWI, Diffusion Weighted Imaging, white matter, brain imaging, neuropsychological performance, neurocognitive performance, structural connectivity

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## 1. INTRODUCTION

Between the years of 2000 and 2015, military personnel have sustained over 327,000 traumatic brain injuries (TBIs) (DVBIC Report, 2015). Of these injuries, the vast majority, exceeding 82% of all TBIs, are in the mild category. In addition to the impact on military readiness, mild traumatic brain injury (mTBI) represents a major health concern and economic burden in the United States [1]. While most individuals who sustain an mTBI will recover fully within a matter of days [2], a significant proportion of individuals with mild TBI will experience a prolonged recovery with persistent post-concussive symptoms, and it is yet unclear why some individuals will show a good injury outcome, whereas other will not [3-6]. Structural damage to white matter axonal tracts has been suggested to underlie many of these persistent behavioral changes [7-11]. Yet due to differences in brain imaging methods, neuropsychological testing approaches, and sample characteristics, this has not been consistently demonstrated at different recovery stages. Furthermore, the relationship between structural connectivity, functional connectivity and neuropsychological performance remains unclear. The present study aims to systematically assess structural connectivity, functional connectivity and neuropsychological functioning at five recovery stages (i.e., two weeks, one month, three months, six months and 12 months) following mild TBI relative to healthy controls. We hypothesize that structural white matter tract disintegrity will underlie abnormalities in functional connectivity, neurocognitive performance and post-concussion symptom severity, but that these metrics will vary with time since injury. The primary aim of the proposed study is therefore to investigate whether measures of white matter disintegrity following mild TBI would explain abnormalities in functional connectivity of the brain, cognition and emotional disturbance, and whether white matter integrity (or lack thereof) could serve as a reliable biomarker of mild TBI. This will allow conclusions on the utility of measures of white matter integrity in the diagnosis of mild TBI. As the study incorporates five time points of measurement to represent different recovery stages of mild TBI, this will allow conclusions on the natural recovery course of mild TBI and the utility of white matter integrity measures in the prediction of injury outcome. In brief, we aim to collect data from 180 participants, including 30 healthy controls and five separate samples of 30 participants at various time points following injury, ranging from 2 weeks to one year post-concussion (see Figure below). During this cross sectional study, participants will attend a single assessment session comprising a series of neuroimaging scans, including diffusion tensor imaging (DTI), structural volumetric scan, and resting state functional connectivity (rsFC). Additionally, participants will also undergo a comprehensive neuropsychological assessment battery. We will analyze differences in structural and functional connectivity across these various stages of recovery and associated differences in neurocognitive performance and symptom expression.


Basic Study Design. A total of 180 participants will be assessed. Six (6) groups of 30 participants with mTBI will be scanned at various time points ranging from 2-weeks to 12-months post-injury. We will also collect diffusion weighted scans from 30 healthy controls (HC).

## 2. KEY WORDS

TBI, traumatic brain injury, concussion, DWI, Diffusion Weighted Imaging, white matter, brain imaging, neuropsychological performance, neurocognitive performance, structural connectivity

## 3. ACCOMPLISHMENTS

The project is progressing and recruitment efforts are ongoing. As we are still a few years from completion, we only report on preliminary analyses at this point. Below, we address each of the major tasks outlined in the revised Statement of Work (SOW) and the accomplishments *this past year:*

**Major Task 1: Study Preparation, Staff Hiring, and Materials Acquisition—COMPLETED**

**Major Task 2: Human subjects approval--COMPLETED**

**Major Task 3: Advertisement and subject recruitment—ONGOING**

**Accomplishments:**

- Recruitment activities remain vigorous and ongoing.
- We continue to establish relationships with several local businesses and community service locations throughout Tucson. We have made contact with local physical therapy offices, collegiate sports head coaches, martial arts businesses, and self-defense classes. We are also currently in the process of gaining permission to access the EPIC medical database at Banner University Medical Center. With this we will be able to reach out to any individuals who have been admitted to the Emergency Department of the hospital with a concussion. We have also reached out and established a relationship with two major community service locations in the city of Tucson: COPE Community Services and La Frontera Arizona. We have additionally established relationships with city adult sports leagues and sports complexes such as: Tucson Women's Soccer League, Maracana Indoor Sports Arena, and Tucson Indoor Sports Center. We have also employed digital means of distribution of our recruitment materials through various University of Arizona listservs.
- We have also continued participant phone recruitment and have screened 255 participants (133 males and 122 females) over the past annual reporting period. Of these individuals, 39 were determined to be eligible and 216 were deemed ineligible. Of those who were eligible, 35 were enrolled in and have completed the study this past year. Four remaining individuals are eligible but have not returned our attempts at communication or have otherwise been unable to schedule an appointment due to a scheduling conflict and/or other commitments.
- Cumulatively, we have phone screened a grand total of 370 individuals since the study's opening at the University of Arizona. Of these, a total of 49 have been eligible to participate. Of those, 47 have been enrolled in and have completed the study. One major challenge has been obtaining head injury documentation for eligible participants, which we require in order for them to become fully enrolled subjects. We have addressed this issue by recently incorporating a generic electronic template form that can be signed by injury witnesses (e.g. coaches, physical therapists/ athletic trainers, or medical professionals).

**Major Task 4: Data collection—ONGOING**

**Accomplishments:** Since starting data collection at the University of Arizona, 38 new participants have now completed all aspects of the study (16 healthy controls, 5 at two weeks post-injury, 6 at one month post-injury, 4 at three months post-injury, 2 at six months post-injury, 5 at 12 months post-injury), yielding 38 complete data sets of neuroimaging and neuropsychological data. No negative outcomes have been reported.

**Major Task 5: Quality Control Checks—ONGOING**

**Accomplishments:**Consistent with the SOW, all data are being uploaded into analysis computers, pre-processed, and checked for errors in acquisition as they are collected. The Lab Manager is overseeing compliance of IRB/HRPO regulations via periodic audit of data storage and test administration by study staff. Behavioral data are being entered and cross-validated for errors by Research Technicians, and all collected data are being backed-up routinely.

**Major Task 6: Preliminary Analyses—ONGOING**

**Accomplishments:** At this point, we have conducted the diffusion tensor imaging (DTI) analysis of all of the 27 mTBI participants whose data was collected at McLean Hospital. We have also performed functional connectivity analysis of 27 participants (3 healthy controls and 24 mTBI survivors) whose data was collected at McLean and 34 participants (19 healthy controls and 15 mTBI survivors) whose data is collected recently (until 31$^{st}$ August 2016) at UA. Below, we describe in detail our preliminary findings showing significant differences of functional connectivity maps for DMN between healthy controls and mTBI participants during their early and late stage of TBI onset and also just within mTBI sample alone (early and late stage of mTBI).

Previously, it has been reported that TBI causes anatomical damage as well as functional damage to brain [12]. Earlier, using diffusion tensor imaging (DTI) techniques, we detected structural changes occurring during early (before 3 months) and late (after 3 months) stages of mTBI. In last year's annual report, we reported significantly lower fractional anisotropy (FA) values in the later stage of mTBI as compared to earlier stage. Considering functional aspects, using voxel based morphometry (VBM) approach, we found that the grey matter volume in the right inferior temporal cortex and ventromedial prefrontal cortex significantly correlated with time since injury, which was also described in last year's annual report.

In order to further explore the functional aspects, we used resting-state functional MRI (rsfMRI) data collected from mTBI survivors to identify different neural networks distributed throughout the whole brain. Depending on the time since mTBI onset from the date of scan, we divided our data set in two categories: (1) 'Early Stage (ES)' for mTBI survivors who suffered a TBI within the last 3 months and (2) 'Late Stage (LS)' for mTBI survivors who suffered a TBI more than 3 months ago.

The primary focus of rsfMRI is on spontaneous low frequency (< 0.1 Hz) oscillations. For the current study, we opted for rsfMRI data over task-based MRI data because clinically it is important to assess the functional role of different brain networks whereas task based MRI data allows to explore the functionality of specific networks depending on the type of stimulus.

In previous studies, using various approaches, several major resting state functional networks were detected and analyzed [13-15]. In a study by Raichle in 2011 [15], using a seed-based approach, seven major resting-state networks were reported. So before comparing and detecting the significant differences between functional connectivity measures for healthy controls and mTBI survivors, we first validated the resting-state networks for healthy-controls using the seed-voxel approach. In seed-voxel approach, a specific brain area is selected as a seed-region and the mean time-series over the voxels of the seed is correlated with each voxel of the brain. Here, we selected seven seed-regions based on a previous study [15].

**Data collection**

Since starting data collection, we currently (as of 08/31/2016) have functional MRI data from (i) 24 mTBI survivors (13F, 11M, mean age = 23.5±5.4 years, 12 ES and 12 LS mTBI survivors with mean age of 21.4±1.7 and 25.6±7 years respectively) (functional MRI data from 2 mTBI survivors out of a total of 26 were discarded as the data were not saved correctly) and 3 healthy controls (all females, mean age = 24.3±2.3 years) - collected at McLean hospital and (ii) 19 mTBI patients (10F, 9M, mean age = 23.5±6.7 years, 13 ES, 6 LS mTBI survivors with mean age of 21±1.1 and 24.7±7.9 years respectively) and 15 healthy controls (9F, 6M, mean age = 22.8±3.4 years) - collected at University of Arizona (UA), comprising a total data collected from 43 mTBI survivors (23F, 20M, mean age = 23.5±5.9 years, 25 ES and 18 LS mTBI survivors with mean age of 21.2±1.5 and 25.1±7.4 respectively) and 18 healthy controls (12F, 6M, mean age = 23.0±3.3 years).

Along with brain imaging data, we also collected behavioral data during cognitive screening of participants, such as: Epworth Sleepiness Scale (ESS), which is a measure of participant's sleepiness (measured during day-time), and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) attention index, which is a measure of participant's attention (coding and digit span indices).

**Approach**

Based on a previous study, for resting-state functional connectivity analysis, we selected seven seed regions: PCC (posterior cingulate cortex), DMPFC (dorsal medial prefrontal cortex), DAC (dorsal anterior cingulate), LMC (left motor-cortex), LV1 (left primary visual), LA1 (left primary auditory) and LFEF (left frontal eye field) (Table 1), which are well known for generating seven individual resting-state functional networks. For seed-voxel functional connectivity analysis, we used MATLAB and SPM (Statistical Parametric Mapping: http://www.fil.ion.ucl.ac.uk/spm/) based functional connectivity toolbox: CONN [16], which also involves basic fMRI data preprocessing steps.

Our goal here was to first validate previously known resting-state networks (RSNs) for healthy controls. Further, for each of the RSN, our goal is to compare and detect the significant difference for strength of functional connectivity between (i) healthy controls and ES mTBI survivors, (ii) healthy controls and LS mTBI survivors and (iii) ES and LS mTBI survivors. In this report, we are reporting the functional connectivity differences for only one of the seven resting-state networks we detected for healthy controls, followed by detecting any behavioral differences between HCs, ES and LS mTBI survivors.

**Findings: Resting state functional networks (RSNs)**

***Healthy controls (HCs)***

For validation of resting-state networks (RSNs), we performed seed-voxel functional connectivity analysis for 15 healthy controls whose data was collected at University of Arizona (UA). Table 1 and figure 1 show a summary of seven resting-state functional networks detected for validation purpose. We found that all the RSNs were consistent with previously reported networks [15].

**Table 1**

| Resting-state Network (RSN) | Networks | Seed Region (MNI co-ordinates) |
|---|---|---|
| RSN01 | Default mode network | PCC (0, -52, 27) |
| RSN02 | Executive control network | DMPFC (0, 24, 46) |
| RSN03 | Salience network | DAC (0, 21, 36) |
| RSN04 | Sensorimotor network | LMC (-39, -26, 51) |
| RSN05 | Visual network | LV1 (-7, 83, 2) |
| RSN06 | Auditory network | LA1 (-62, -30, 12) |
| RSN07 | Dorsal attention network | LFEF (-29, -9, 54) |

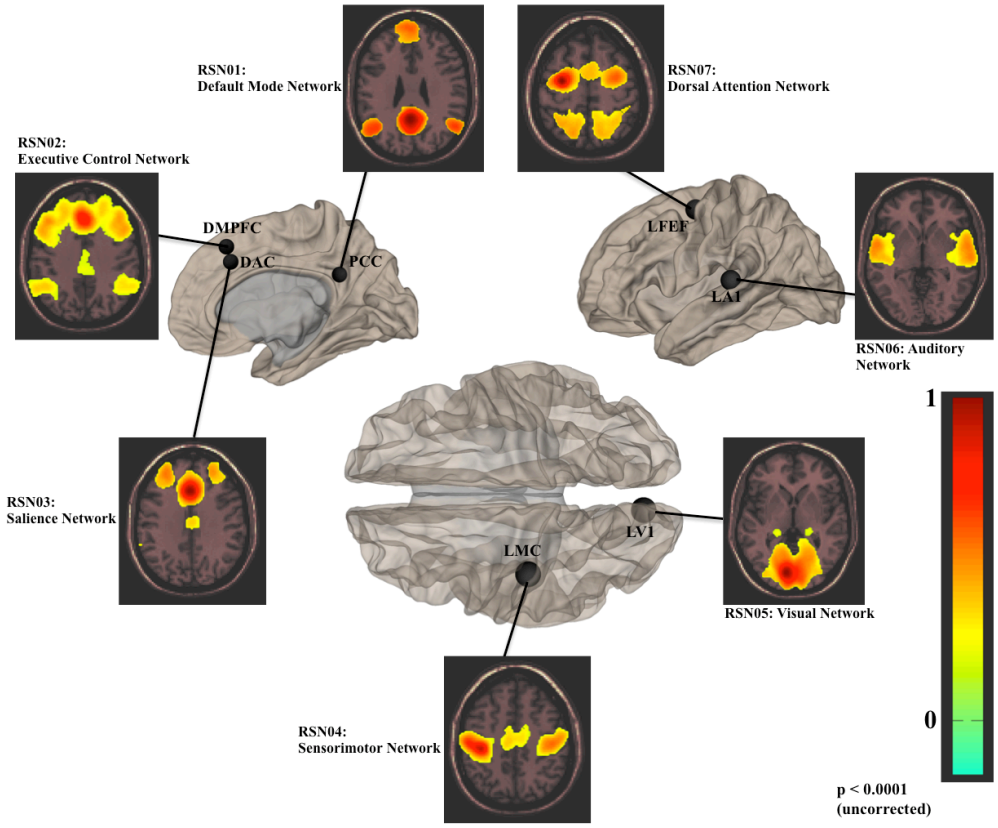


**Figure 1.** Here we summarize seven RSNs, corresponding to seven seed regions (Table 1) detected for healthy controls.

***Resting-state functional connectivity: Healthy controls (HCs), Early Stage (ES) and Late Stage (LS) Traumatic Brain Injury (TBI) survivors***

For HCs, figure 2A shows the significant functional connectivity patterns on brain surface for RSN01: default mode network (DMN), considering PCC as a seed region. In table 2, we report the sites in detail showing these functional connectivity patterns.

**Table 2**

| **Sites of significant functional connectivity*** | **Peak MNI Co-ordinates** | | | **Cluster size (number of voxels)** | **T-score** |
|---|---|---|---|---|---|
| | X | Y | Z | | |
| ***Seed PCC: HCs*** | | | | | |
| Precuneus (28%) and posterior cingulate gyrus (37%) | 0 | -50 | 28 | 2892 | 29.59 |
| Left angular gyrus (28%) and left lateral occipital cortex (9%) | -46 | -60 | 32 | 782 | 13.84 |
| Right angular gyrus (20%) and right lateral occipital cortex (4%) | 56 | -62 | 28 | 568 | 12.91 |
| Left medial frontal cortex (37%) and left paracingulate gyrus (5%) | -6 | 40 | -18 | 521 | 10.31 |
| Left middle temporal gyrus (anterior, 48% and posterior, 4%) | -50 | -6 | -26 | 349 | 9.94 |
| Paracingulate gyrus (left, 4% and right, 5%) | -10 | 48 | 20 | 221 | 8.77 |
| Right middle temporal gyrus (anterior, 17% and posterior, 3%) | 56 | -8 | -22 | 144 | 9.63 |
| Right insular cortex (4%) | 34 | 16 | -2 | 57 | -8.08 |
| Right insular cortex (3%) | 46 | 6 | -6 | 35 | -8.56 |

*Height threshold, $p < 0.001$, FD-corrected; *Extent threshold, $p < 0.001$, FDR-corrected.

*(a) ES mTBI survivors*

For ES mTBI survivors, figure 2B shows the significant functional connectivity patterns on brain surface. In table 3, we report the sites in detail showing these functional connectivity patterns.

**Table 3**

| Sites of significant functional connectivity* | Peak MNI Co-ordinates | | | Cluster size (number of voxels) | T-score |
|---|---|---|---|---|---|
| | X | Y | Z | | |
| ***Seed PCC: ES mTBI*** | | | | | |
| Left medial frontal cortex (88%), paracingulate gyrus (left, 59% and right, 46%), left superior frontal gyrus (39%), frontal pole (left, 32% and right 20%), left anterior cingulate gyrus (29%), left middle frontal gyrus (21%) and left subcallosal cortex (47%) | -2 | 60 | -16 | 13541 | 17.56 |
| Posterior cingulate gyrus (78%), precuneous (59%), left posterior parahippocampal cortex (58%) and left hippocampus (30%) | 0 | -52 | 26 | 8310 | 26.03 |
| Right inferior frontal gyrus (57%), right frontal operculum cortex (80%) and right insular cortex (38%) | 36 | 50 | 34 | 3272 | -10.02 |
| Left middle temporal gyrus (anterior, 67% and posterior, 84%) | -66 | -18 | -20 | 2843 | 15.85 |
| Left angular gyrus (52%) and left lateral occipital cortex (26%) | -44 | -70 | 38 | 2243 | 16.22 |
| Right middle temporal gyrus (anterior, 98%, posterior, 44%), right temporal pole (17%), and right inferior temporal gyrus (anterior, 25%) | 60 | 0 | -26 | 1977 | 14.48 |
| Right angular gyrus (33%) and right lateral occipital cortex (18%) | 56 | -64 | 34 | 1735 | 12.48 |
| Left frontal operculum cortex (66%) and left insular cortex (33%) | -40 | -8 | -16 | 1383 | -9.98 |
| Right supramarginal gyrus (anterior, 48% and posterior, 35%) | 66 | -42 | 34 | 1183 | -10.10 |
| Left supramarginal gyrus (anterior, 61% and posterior, 10%) | -52 | -38 | 52 | 957 | -8.96 |
| Right parahippocampal gyrus (50%) and right hippocampus (28%) | 24 | -14 | -20 | 537 | 8.68 |

*Height threshold, $p < 0.001$, FD-corrected; *Extent threshold, $p < 0.001$, FDR-corrected.

*(b) LS mTBI survivors*

For LS mTBI survivors, figure 2C shows the significant functional connectivity patterns on brain surface. In table 4, we report the sites in detail showing these functional connectivity patterns.

**Table 4**

| Sites of significant functional connectivity* | Peak MNI Co-ordinates | | | Cluster size (number of voxels) | T-score |
|---|---|---|---|---|---|
| | X | Y | Z | | |
| ***Seed PCC: LS mTBI*** | | | | | |
| Frontal pole (left, 22% and right, 15%), superior frontal gyrus (left, 22% and right, 14%), paracingulate gyrus (left, 44% and right, 34%), left medial frontal cortex (56%), left anterior cingulate gyrus (7%) and left subcallosal cortex (12%) | -8 | 58 | 34 | 7186 | 16.79 |
| Precuneous (35%), posterior cingulate gyrus (57%) | 0 | -52 | 28 | 3974 | 23.50 |
| Left middle temporal gyrus (anterior, 76% and posterior, 61%) and left temporal pole (16%) | -66 | -12 | -20 | 1998 | 14.22 |
| Right temporal pole (22%), right middle temporal gyrus (anterior, 85% and posterior, 23%) and right inferior temporal gyrus (anterior, 16%) | 44 | 20 | -38 | 1494 | 11.85 |
| Left angular gyrus (29%) and left lateral occipital cortex (20%) | -44 | -56 | 32 | 1464 | 15.23 |
| Right angular gyrus (16%) and right lateral occipital cortex (11%) | 50 | -62 | 32 | 991 | 14.11 |
| Left middle frontal gyrus (10%) | -36 | 12 | 54 | 305 | 12.46 |
| Left supramarginal gyrus (anterior, 24%) | -56 | -36 | 48 | 266 | -8.68 |
| Right frontal operculum cortex (24%) and right insular cortex (9%) | 38 | 20 | -2 | 194 | -8.29 |
| Left hippocampus (9%) and left parahippocampal cortex (anterior, 7% and posterior 7%) | -22 | -18 | -30 | 166 | 9.01 |
| Left frontal operculum cortex (16%) and left insular cortex (4%) | -28 | 16 | 6 | 111 | -7.97 |
| Right supramarginal gyrus (anterior, 6% and posterior, 1%) | 56 | -36 | 52 | 78 | -6.96 |
| Right inferior frontal gyrus (9%) | 52 | 8 | 8 | 72 | -8.57 |

*Height threshold, $p < 0.001$, FD-corrected; *Extent threshold, $p < 0.001$, FDR-corrected.

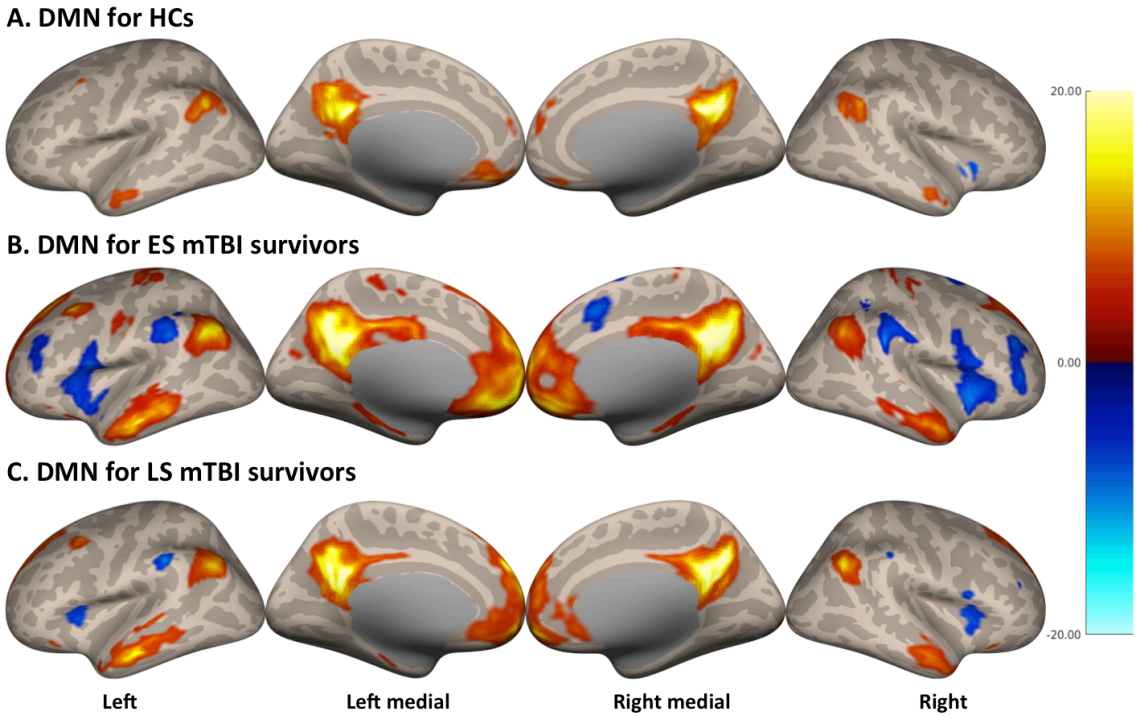



**Figure 2.** Functional connectivity maps generated for DMN (height threshold, $p < 0.001$, FD-corrected; extent threshold, $p < 0.001$, FDR-corrected), considering posterior cingulate cortex (PCC) as seed region for (A) Healthy Controls (HCs) (B) ES and (C) LS mTBI survivors.

In tables 2, 3 and 4 above, we report the common functional connectivity maps (i) among HCs, ES and LS mTBI survivors in 'green' color, (ii) between ES and LS mTBI survivors in 'blue' color whereas the functional connectivity maps which are not common in any case are colored in 'red'. Here, we noticed hyper connectivity (large percent of functional connectivity maps) in ES mTBI case, but with time this percent decreases with time (LS case) and tends towards normal percent connectivity maps (HCs case) (Figure 3A). In figure 3A, we showed the percent involvement of only those regions, which were common between HCs, ES and LS mTBI survivors but showed at-least 25% involvement in HCs. On the other hand, in figure 3B, we showed the decrease in percent involvement of only those regions, which were common between ES and LS mTBI survivors but showed at-least 20% involvement in LS mTBI survivors.

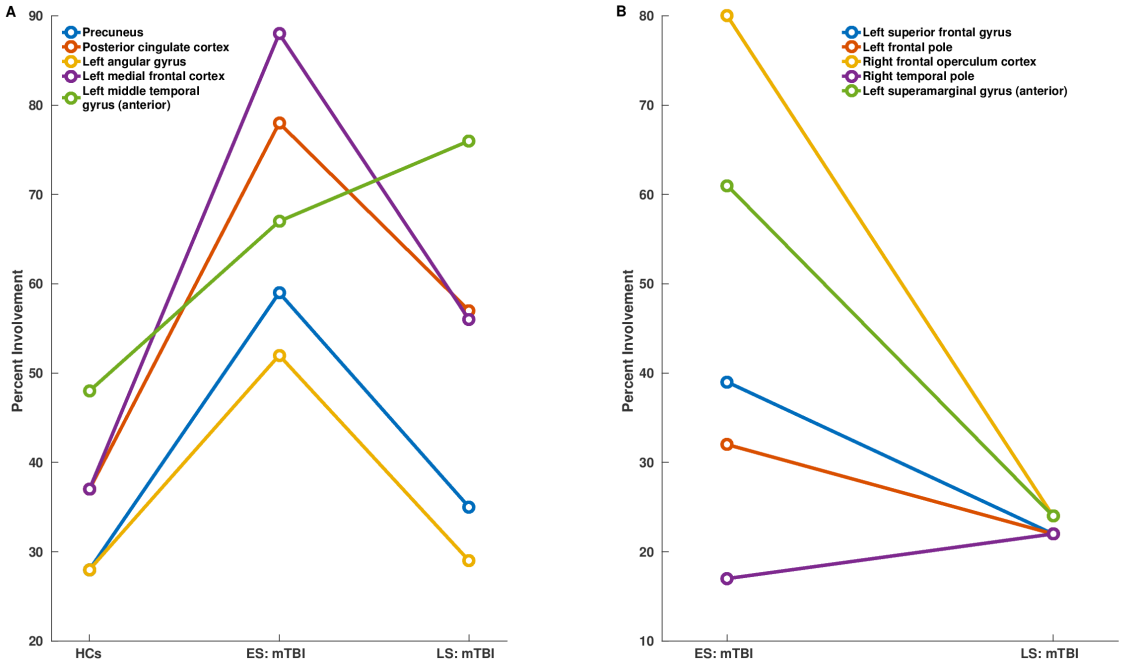



**Figure 3.** Comparison of percent involvement of regions involved significantly (tables 2, 3 and 4) in functional connectivity maps of DMN between (A) healthy controls (HCs), ES and LS mTBI survivors and (B) ES and LS mTBI survivors.

*(c) HCs versus ES mTBI survivors*

Further, we computed the significant differences between functional connectivity patterns of HCs and ES mTBI survivors for DMN. Figure 4A shows these significant differences on brain surface. In table 5, we report the sites in detail showing these significantly different functional connectivity clusters.

**Table 5**

| **Sites of significant functional connectivity*** | **Peak MNI co-ordinates** | | | **Cluster size (number of voxels)** | **T-score** |
|---|---|---|---|---|---|
| | X | Y | Z | | |
| ***Seed PCC: ES > HCs*** | | | | | |
| Right supplementary motor cortex (3%), anterior cingulate cortex (1%), | 14 | 0 | 44 | 75 | 5.38 |
| Left insular cortex (2%), left central opercular cortex (1%) | -32 | -16 | 12 | 50 | 5.36 |
| Anterior cingulate cortex (1%), left supplementary motor cortex (1%) | -6 | -6 | 40 | 34 | 5.03 |
| Right post-central gyrus (1%), right pre-central gyrus (11 voxels), | 46 | -16 | 34 | 33 | 4.21 |
| Left pre-central gyrus (17 voxels) | -22 | -24 | 76 | 19 | 4.29 |
| Right inferior temporal gyrus (posterior, 2%) | 58 | -36 | -20 | 19 | 4.10 |
| Left hippocampus (2%) | -28 | -12 | -18 | 16 | 5.17 |
| Left pre-central gyrus (12 voxels), left post-central gyrus (1 voxel) | -44 | -12 | 36 | 13 | 4.11 |

| | | | | | |
|---|---|---|---|---|---|
| Left middle temporal gyrus (anterior, 2%) | -58 | -10 | -14 | 11 | -4.14 |

*Height threshold, p < 0.001, FDR un-corrected; *Cluster size > 10.

*(d) HCs versus LS mTBI survivors*

Further, we computed the significant differences between functional connectivity patterns of HCs and LS mTBI survivors for DMN. Figure 4B shows these significant differences on brain surface. In table 6, we report the sites in detail showing these significantly different functional connectivity clusters.

**Table 6**

| **Sites of significant functional connectivity*** | **Peak MNI Co-ordinates** | | | **Cluster size (number of voxels)** | **T-score** |
|---|---|---|---|---|---|
| | X | Y | Z | | |
| ***Seed PCC: LS > HCs*** | | | | | |
| Right precentral gyrus (1%), right middle frontal gyrus (12 voxels) | 54 | 10 | 40 | 59 | 4.66 |
| Left insular cortex (1%) | -34 | -6 | -6 | 14 | 4.32 |
| Left central opercular cortex (1%), left insular cortex (2 voxels) | -38 | -8 | 18 | 11 | 4.19 |

*Height threshold, p < 0.001, FDR un-corrected; *Cluster size > 10.

*(e) ES versus LS mTBI survivors*

Next, we also computed the significant differences between functional connectivity patterns of ES and LS mTBI survivors for DMN. Figure 4C shows these significant differences on brain surface. In table 7, we report the sites in detail showing these significantly different functional connectivity clusters.

**Table 7**

| **Sites of significant functional connectivity*** | **Peak MNI Co-ordinates** | | | **Cluster size (number of voxels)** | **T-score** |
|---|---|---|---|---|---|
| | X | Y | Z | | |
| ***Seed PCC: ES > LS*** | | | | | |
| Left pre-central gyrus (2%), left post-central gyrus (11 voxels) | -24 | -26 | 68 | 133 | 4.47 |
| Right temporal pole (3%) | 40 | 16 | -38 | 75 | -4.85 |
| Right middle temporal gyrus (posterior, 2% and temporo-ccipital, 1%), right superior temporal gyrus (posterior, 3%), right supramarginal gyrus (posterior, 1%) | 58 | -32 | 4 | 62 | -4.40 |
| Left middle temporal gyrus (anterior, 9% and posterior, 3 voxels) | -56 | -10 | -12 | 46 | -4.70 |
| Left inferior frontal gyrus 3%), left pre-central gyrus (4 voxels), left central opercular cortex (4 voxels), left frontal opercular cortex (1 voxel) | -50 | 6 | 4 | 41 | -5.05 |
| Left temporal pole (1%), left superior temporal gyrus (anterior, 3 voxels) | -46 | 6 | -16 | 35 | -5.14 |
| Right supramarginal gyrus (posterior, 1% and | 66 | -38 | 30 | 23 | -4.28 |

| | | | | | |
|---|---|---|---|---|---|
| anterior, 3 voxels) | | | | | |

*Height threshold, p < 0.001, FDR un-corrected; *Cluster size > 10.

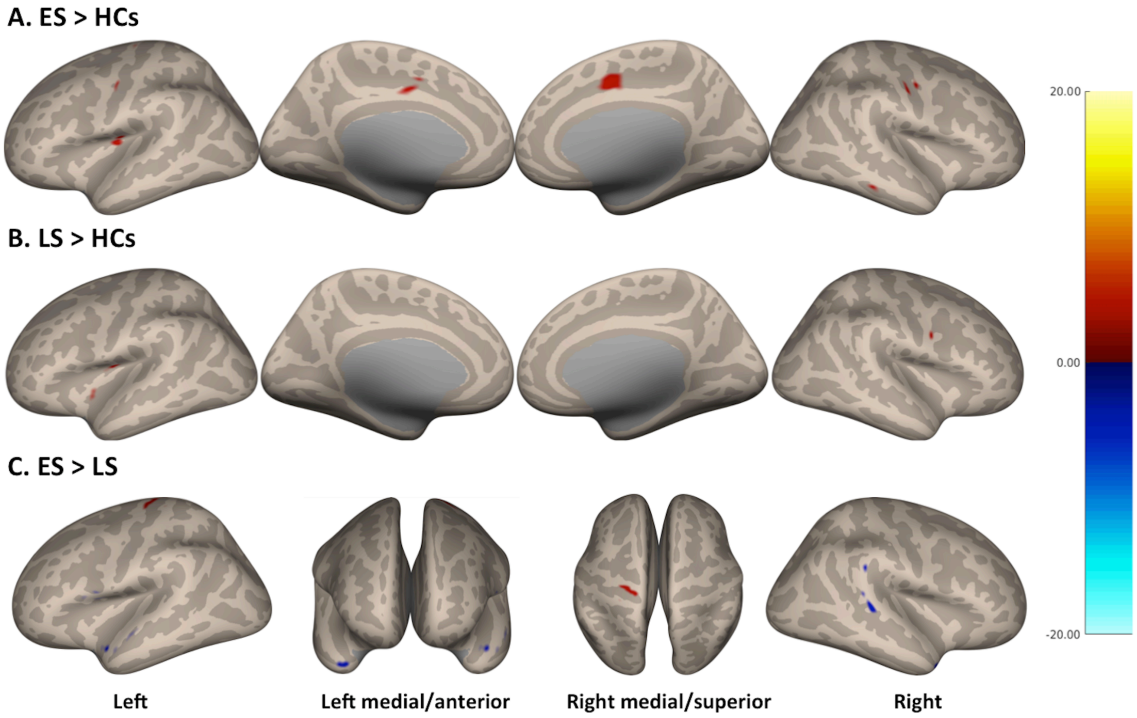



**Figure 4.** Significant differences between functional connectivity maps generated for DMN (height threshold, p < 0.001, FDR un-corrected; cluster size > 10), considering posterior cingulate cortex (PCC) as seed region for (A) ES mTBI survivors > HCs (B) LS mTBI survivors > HCs and (C) ES mTBI survivors > LS mTBI survivors.

**Behavioral differences between HCs, ES and LS mTBI survivors**

We compared ESS and RBANS scores between HCs, ES and LS mTBI survivors (Figure 5). *ESS scores:* We found strong significant difference between ESS scores for HCs and ES mTBI survivors (two-sample t-test, p < 0.01). There was also significant difference between ESS scores for HCs and LS mTBI survivors (two-sample t-test, p < 0.05) but less stronger than between HCs and ES mTBI survivors, although there was still no significant difference between ESS scores for ES and LS mTBI survivors (two-sample t-test, p > 0.05).

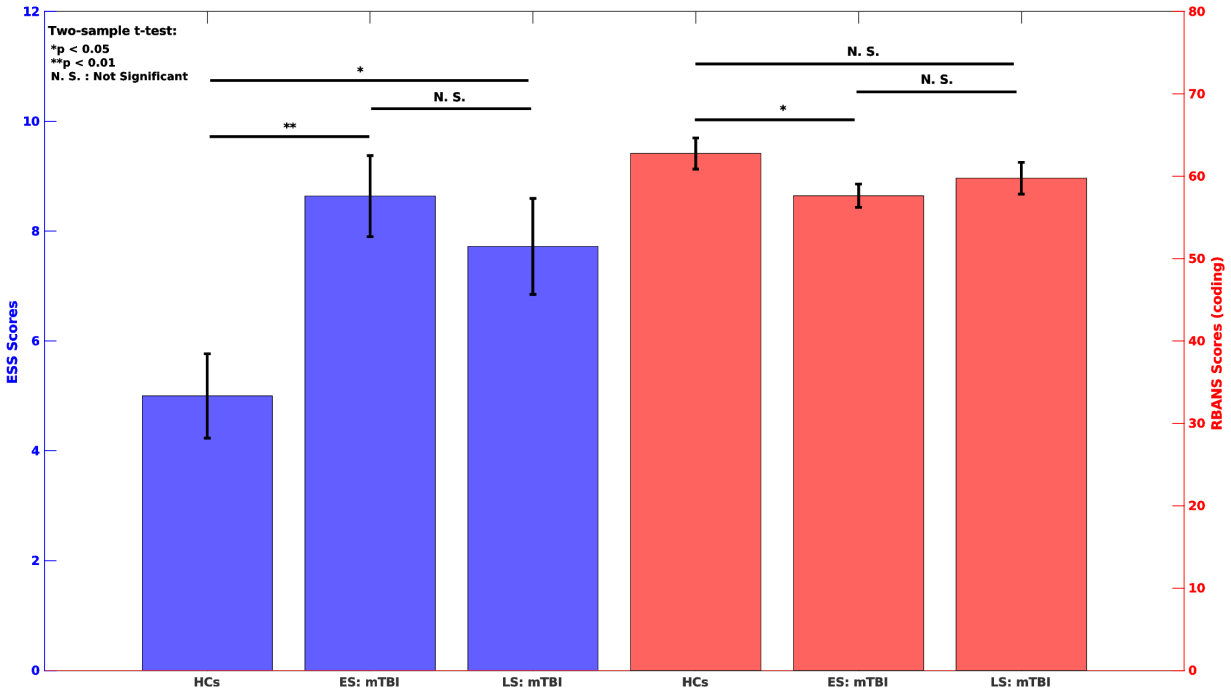



**Figure 5.** Comparison of ESS and RBANS scores (coding) between HCs, ES: mTBI and LS: mTBI survivors.

*RBANS scores:* We did not find any significant difference between RBANS digit span scores for HCs, ES or LS mTBI survivors. But there was significant difference between RBANS coding scores (two-sample t-test, $p < 0.05$) for HCs and ES mTBI survivors and there was no significant difference (two-sample t-test, $p > 0.05$) between RBANS coding scores for HCs and LS mTBI survivors.

## Methodological Advances

Multiband Sequence Development. Initial analysis of the multiband sequence suggests that the estimation of scalar parameters such as fractional anisotropy and mean diffusivity are significantly altered relative to the scan without multiband as presented in the e-poster presentation "Effects of Multiband Acceleration on High Angular Resolution Diffusion Imaging Data Collection, Processing and Analysis" at the 2016 ISMRM in Singapore. However, the fiber orientations estimated from both accelerated and unaccelerated are similar. Further analysis is being done to evaluate the repeatability of multiband scans on a single subject. As suggested previously, a 3-shell acquisition with b=1000, 2000, and 3000 s/mm^2 has been incorporated into the sequence which will allow for more sophisticated analysis to be run on the data in addition the increased ability to identify complex fiber crossing patterns. From the data, the mean apparent propagator of water diffusion can be estimated, and parameters that more completely characterize the microstructural environment can be determined, ideally providing more sensitive and specific measures of change in instances of disease.

Processing Pipeline for DTI. The preprocessing pipeline remains largely the same. Echo planar imaging distortions are reduced using FSL's TOPUP routine, eddy-current distortions and

motion correction is then performed using FSL's EDDY, and local principal component analysis is performed using in-house MATLAB software. Multiple options for performing fiber tractography and other analysis are being considered, including TRACULA from FreeSurfer, which is a unique global tractography technique based on prior knowledge of several existing neural pathways, MRTrix which uses the constrained spherical deconvolution technique to better resolve crossing fibers and then perform tractography, DSI studio which uses generalized q-sampling imaging to fit multishell datasets and perform tractography, and finally, in house MATLAB software is used to estimate the mean apparent propagator.

**Preliminary Analysis Conclusions**

From functional connectivity maps of HCs and mTBI survivors, we found that there was hyper connectivity within default mode network following the brain injury (within 3 months of the onset of injury) but with time this hyper connectivity tends to be normal towards HCs for the mTBI survivors who had brain injury onset since more than 3 months.

From direct calculation of significant functional connectivity differences between HCs and mTBI survivors, we also noticed that there was clear abnormally high hyper connectivity at the early stage of mTBI survivors, compared to HCs and late stage mTBI survivors but there were also very few small sized clusters found with percent involvement of around 1% or lesser which showed stronger functional connectivity for late stage mTBI survivors compared to HCs. This could either be a sign of neural plasticity or could still reflect abnormal hyper connectivity for LS mTBI survivors.

Comparison of ESS and RBANS scores also confirmed our findings from functional connectivity analysis. We found that there was significant improvement in ESS scores with time i.e. late stage mTBI survivors were found to be less sleepy during daytime, along with being more attentive than mTBI survivors who were in their early stage.

**Major Task 7: Extensive Data Analysis—PENDING FINAL DATA COLLECTION**

**Accomplishments:**

- Nothing to report

**Major Task 8: Manuscript Preparation and Submission for Publication—ONGOING**

**Accomplishments:**

- During the past year, we have published several peer-reviewed articles, book chapters, and conference abstracts, as outlined below in section 6:

**Opportunities for Training and Professional Development**

While the primary goal of this project is not to provide training and professional development, many such experiences have occurred for our team members. The present project has supported:

4 members of our lab attended lectures and presented research findings at the International Neuropsychological Society Meeting, Boston, MA, February 3-6, 2016

3 members of our lab attended lectures and presented research findings at the Society of Biological Psychiatry Meeting, Atlanta, GA, May 12-14, 2016

4 members of our lab attended lectures and presented research findings at the Associated Professional Sleep Societies Meeting, Denver, CO, June 11-15, 2016

1 member of our lab attended lectures and presented research findings at the Military Health Systems Research Symposium, Orlando, FL, August 15-18, 2016.

1 member of our lab attended lectures and presented research findings at the meeting of the Society for Psychophysiological Research, Minneapolis, MN, September 21-25, 2016.

1 member of our lab attended a workshop entitled: Sleep Health Scoring for the Polysomnographer, Scottsdale, AZ, October 13-14, 2016.

1 member of our lab attended a workshop entitled: Actigraphy and Figness/Sleep trackers in Adults and Children: Fundamentals and applications, at the Associated Professional Sleep Societies Meeting, Denver, CO, June 11-15, 2016

1 postdoc attended the Mind Research Network Functional MRI Training Workshop (Jan 2016) in Albuquerque, NM.

1 postdoc and 1 graduate student attended the CONN Functional Connectivity Workshop (April 2016), in Boston, MA.

2 postdocs attended the NIH Grant Writing Workshop at the University of Arizona (August 2016), Tucson, AZ.

1 postdoc attended the Applied Workshop on the New SCID-5, Mastering the Diagnostic Interview, University of Michigan.

Multiple members of our lab have attended regular training in MRI analysis methods and safety as part of an ongoing training series offered at the University of Arizona.

Multiple members of our lab receive regular one-on-one instruction and supervision in the administration and scoring of neuropsychological assessments, psychodiagnostic testing, electrode placement, and patient interviewing.

Over 15 members of our lab have undergone regular in-house training in the use of various brain-imaging software, including SPM12, Matlab, FSL, Freesurfer, TracVis, MRIcron and others.

Over 15 members of our lab have undergone basic training modules in ethical conduct, statistical analysis, and neuroanatomy.

**Dissemination to Communities of Interest**

We have worked to disseminate knowledge about mild traumatic brain injury and our current study to a number of interested communities. Notably, we have given a presentation to the Tucson Veteran's Center regarding TBI and the studies we have ongoing. Our staff has also made several short presentations to the medical residents at the University of Arizona Medical Center, the local athletics department, and seminars at various colleges in the university over this past year. We have presented some elements of these findings to military audiences at the Military Health Systems Research Symposium this past year, as well as several conferences on topics such as neuropsychology, psychiatry, and sleep medicine.

**Plan for Next Reporting Period**

The current plan is to continue with our ongoing recruitment efforts, including radio and print advertisements, in order to maintain a steady flow of participants in the study. We plan to continue evaluating the sources of recruitment and the factors that may be excessively excluding participants. We will continue with educational and outreach efforts to communicate information about mTBI and broaden recruitment efforts within the Tucson and surrounding communities.

## 4. IMPACT

**Impact on the development of the principal discipline(s) of the project?**

Work from this project has led to the refinement of new techniques for acquiring DTI data using multiband sequences. This information was presented at the International Society for Magnetic Resonance in Medicine (IMSRM) earlier this year. Other than that, the results are too preliminary to make wide-ranging impacts.

**Impact on other disciplines?**

Nothing to report.

**Impact on technology transfer?**

Nothing to report.

**Impact on society beyond science and technology?**

Nothing to report.

## 5. CHANGES/PROBLEMS

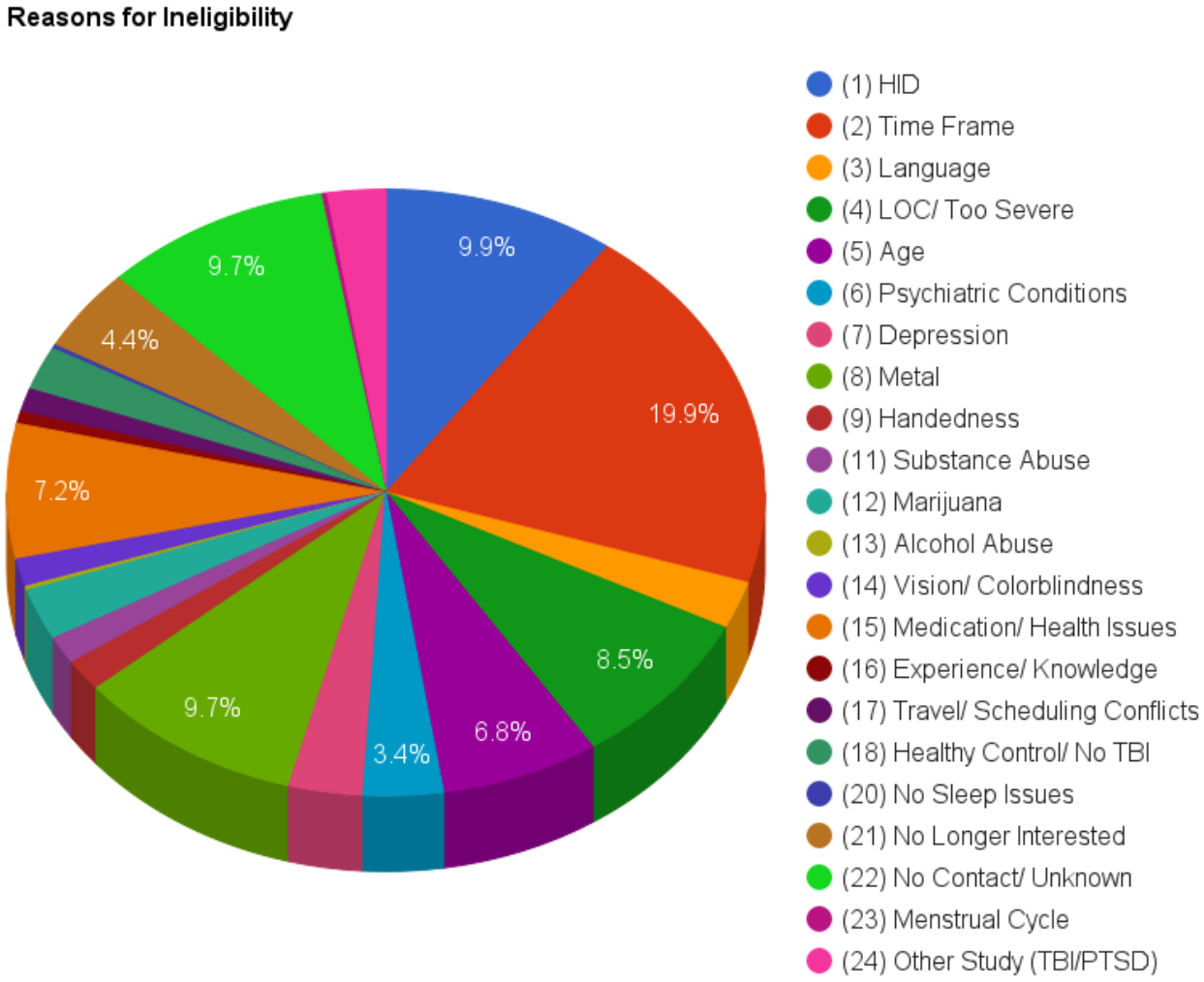
Our major challenge has been recruiting enough eligible participants to reach our quarterly goals. While there have been many individuals who have expressed interest in participating in the study, a number of exclusionary factors have consistently been present that preclude their participation. The major exclusionary elements include: (1) lack of head injury documentation to certify a mild traumatic brain injury; (2) the mild traumatic brain injury occurred beyond 12-month time frame; (3) potential participants have metal in their body, thereby preventing them from undergoing scanning; (4) traumatic brain injury was too severe; (5) potential participants were taking exclusionary medications and/or had serious physical or mental health conditions.

While many exclusionary criteria cannot be modulated, we did make slight alterations in order to allow more participants to complete the study. First of all, because many individuals were being excluded due to psychiatric issues (primarily depression) and accompanying exclusionary medication, we changed our exclusionary mandates so that individuals who started exhibiting symptoms of depression and taking anti-depressants after their concussion would be eligible, barring any other issues with their eligibility. Further, because many current and former athletes have expressed interest in our study, and those individuals tend to have sustained multiple head injuries, we changed the maximum number of concussions that potential participants are allowed to have from 5 to 10.

Another issue that has barred participation for a number of individuals is substance abuse, especially the use of cannabis. Therefore, we have modified our exclusion criteria to permit a more liberal history of cannabis while still excluding for current usage or use that began before the age of 16.

Although we have modulated our exclusion criteria in order to ameliorate the issue of so much ineligibility, we have continued to collect detailed data regarding anti-depressant use, number of concussions sustained, and history or cannabis use so that it can be factored into future scientific data analyses.

In the past year, there have been no changes that have had a significant impact on expenditures, nor any changes to the care of our human subjects.




## 6. PRODUCTS

A number of products, including peer-reviewed journal articles, book chapters, and published conference abstracts have emerged this year, including:

**Peer-Reviewed Articles:**

**Killgore, WDS**, Singh, P, Kipman, M, Pisner, D, Fridman, A, and Weber, M. Gray matter volume and executive functioning correlate with time since injury following mild traumatic brain injury. Neuroscience Letters, 612, 238-244, 2016.

Singh, P, & **Killgore WDS**. Time dependent differences in gray matter volume post mild traumatic brain injury. Neural Regeneration Research, 11, 920-921, 2016.

**Book Chapters:**

Klimova, A, Singh, P, & **Killgore WDS**. White matter abnormalities in MS: Advances in diffusion tensor imaging/tractography. In Watson, RR & Killgore, WD (Eds), Nutrition and

Lifestyle in Neurological Autoimmune Diseases (in press).

**Published Abstracts:**

Singh, P, Pisner, D, Fridman, A, Singh A, Millan, M, & **Killgore, WD.** A voxel based morphometric analysis of ventromedial prefrontal cortex volume related with executive function task performance post mild traumatic brain injury. Abstract presented at the 71st Annual Scientific Convention of the Society for Biological Psychiatry, Atlanta, GA, May 12-14, 2016.

Bernstein, AS, Pisner, D, Klimova, A, Umapathy, L, Do, L, Squire, S, **Killgore, WD**, & Trouard, T. Effects of multiband acceleration on high angular resolution diffusion imaging data collection, processing, and analysis. Abstract presented at the 24th Annual Meeting of the International Society for Magnetic Resonance in Medicine (IMSRM), Singapore, May 7-8, 2016.

Pisner, D, Singh, P, Fridman, A, & **Killgore, WD**. Resilience following mild traumatic brain injury is associated with gray matter volume in the left precentrual gyrus. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

Singh, P, Fridman, A, Pisner, D, & **Killgore, WD.** Time dependent differences in gray matter volume in individuals post mild traumatic brain injury: A voxel based morphometric study. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

Fridman, A, Pisner, D, Singh, P, & **Killgore, WD**. Gray matter volume in left medial prefrontal cortex is related to life satisfaction in individuals with mild traumatic brain injury. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

Singh, P, Pisner, D, Fridman, A, Roberts, S, & **Killgore, WD.** Volumetric differences in gray matter in healthy versus overweight/obese individuals post mild traumatic brain injury: A voxel based morphometric study. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

Singh, P, Fridman, A, Pisner, D, Singh, A, & **Killgore, WD.** A voxel based morphometric analysis of ventromedial prefrontal cortex volume related with executive function task performance post mild traumatic brain injury. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

Klimova, A, Pisner, D & **Killgore, WD**. Neural correlates of cognitive and emotional impairments in acute versus chronic mild traumatic brain injury: a diffusion tensor imaging study. Abstract presented at the 44th Annual Meeting of the International Neuropsychological Society, Boston, MA, February 3-6, 2016.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

**What individuals have worked on the project?**

Name: William D. “Scott” Killgore, Ph.D.
Project Role: PI
Nearest person month worked: 2
Contribution to Project: Oversees all aspects of project progress and orchestrates data analysis and publication efforts.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Anna Alkozei, Ph.D.
Project Role: Postdoctoral Fellow
Nearest person month worked: 3
Contribution to Project: Dr. Alkozei performs data analysis and processing for the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Ryan Smith, Ph.D.
Project Role: Postdoctoral Fellow
Nearest person month worked: 3
Contribution to Project: Dr. Smith performs data analysis and processing for the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Sara Knight
Project Role: Lab Manager
Nearest person month worked: 3
Contribution to Project: Ms. Knight oversees the administrative needs of the study and study staff, in addition to providing regulatory support and performing periodic quality control checks.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Matthew Allbright
Project Role: Research Technician
Nearest person month worked: 3
Contribution to Project: Mr. Allbright oversees the technical aspects of the project and assists in database export, storage, and management.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571

USAMRAA W81XWH-11-1-0056
USAMRAA W81XWH-12-1-0386

Name: Sarah (Markowski) Berryhill
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Mrs. Berryhill provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-16-1-0062
USAMRAA W81XWH-12-1-0386

Name: Andrew Fridman
Project Role: Research Technician
Nearest person month worked: 4
Contribution to Project: Mr. Fridman provides support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Miyla McIntosh
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Ms. McIntosh provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Melissa Millan
Project Role: Research Technician
Nearest person month worked: 4
Contribution to Project: Ms. Millan oversees project progress and manages the day-to-day needs of the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: William Palmer
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Mr. Palmer provided support with data collection and recruitment activities.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

Name: Derek Pisner
Project Role: Research Technician
Nearest person month worked: 2
Contribution to Project: Mr. Pisner previously oversaw project progress and managed the day-to-day needs of the project.
Funding support: USAMRAA W81XWH-14-1-0570
USAMRAA W81XWH-14-1-0571
USAMRAA W81XWH-12-1-0386

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Since the last reporting period, the PI has added effort on two other projects. The first project is funded by USAMRAA W81XWH-16-1-0062 and expires in APR 2020. This grant was previously pending and is now active. The second project is funded by USAMRAA W81XWH-11-1-0056 and expires 31 DEC 2016. This award was pending transfer from the PI's former institution until earlier this year.

**What other organizations were involved as partners?**

Nothing to Report.

## 8. SPECIAL REPORTING REQUIREMENTS

Please see updated Quad Chart attached in Appendix.

## CONCLUSION

The study is now progressing as planned. Although recruitment has struggled due to difficulty obtaining participants with documentation of head injury and injuries that meet our very specific time frame, we continue to advance forward and data collection is ongoing. Preliminary findings suggest that the procedures are working and that valid data is being collected. Data will continue to be collected over the next two years in order to obtain a sufficient sample size to conduct meaningful results.

## REFERENCES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**A Model for Predicting Cognitive and Emotional Health from Structural and Functional Neurocircuitry Following Traumatic Brain Injury**

**Study Tasks and Assessments**

Day of Scan Questionnaire

Epworth Sleepiness Scale (ESS)

OSU TBI Interview

Glasgow Outcome Scale – Extended (GOS-E)

MINI International Psychiatric Interview (MINI)

California Verbal Learning Test (CVLT)

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Delis-Kaplan Executive Function System (D-KEFS)

Go/No Go

Brief Visual Memory Test-Revised (BVMT-R)

Buss Perry Aggression Questionnaire (BPAQ)

Psychomotor Vigilance Test (PVT)

Pittsburgh Sleep Quality Index (PSQI)

State Trait Anxiety Inventory (STAI)

Automated Neuropsychological Assessment Metrics (ANAM)

Beck Depression Inventory (BDI-II)

Wechsler Abbreviated Scale of Intelligence (WASI II)

Connor- Davidson Resilience Scale (CD-RISC)

Craig Handicap Assessment and Reporting Technique Short Form (CHART-SF)

Personality Assessment Inventory (PAI)

Alcohol Use Disorder Identification Test (AUDIT)

Rivermead Post Concussion Symptoms Questionnaire (RPCSQ)

Snaith Hamilton Pleasure Scale (SHAPS)

Satisfaction With Life Scale (SWLS)

Edinburgh Handedness Survey (EHS)

Marijuana Use Questionnaire (MUSE)

# A Model for Predicting Cognitive and Emotional Health from Structural and Functional Neurocircuitry following Traumatic Brain Injury

PT110814

W81XWH-12-1-0386

**PI:** William D. Killgore, Ph.D. **Org:** University of Arizona **Award Amount:** $2,272,098

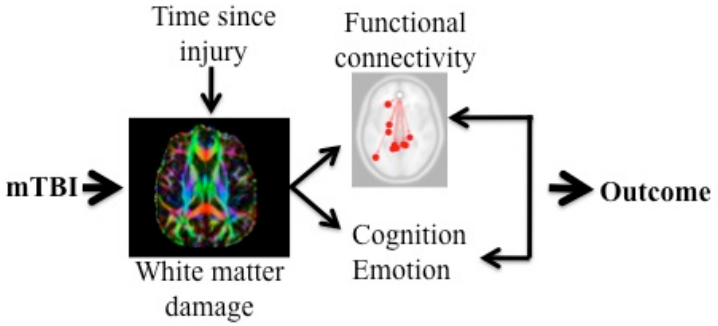
## Study/Product Aim(s)

- Demonstrate the extent to which structural white matter damage explains abnormalities in cognition and emotion at different recovery stages following mild traumatic brain injury (TBI).
- Demonstrate the extent to which structural white matter damage explains abnormalities in functional connectivity at different recovery stages following mild TBI.
- Determine whether white matter disintegrity could serve as an objective marker for mild TBI.

## Approach

Cross-sectional study involves comprehensive neuropsychiatric and neuropsychological assessment of 30 healthy controls and 150 individuals with mild TBI, of which 30 each will be assessed at 2 weeks, 1 month, 3 months, 6 months, and 12 month post-TBI. All participants undergo diffusion-weighted imaging, resting-state functional connectivity imaging, and neurocognitive assessment.

The study investigates whether and how white matter damage at 5 different natural recovery stages contributes to functional connectivity, cognition and emotion.




**Accomplishments**: Study is well underway after transferring from McLean Hospital to University of Arizona. 31 participants were collected at McLean, and 33 have been collected at University of Arizona. Data collection ahead of schedule and 1/3 complete.

## Timeline and Cost

| Activities CY | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|---|
| Study preparations | | | | | | | |
| Data collection | | | | | | | |
| Lab Relocation/Grant Move | | | | | | | |
| Data quality check | | | | | | | |
| Data analysis/dissemination | | | | | | | |
| **Estimated Budget ($2,272K)** | **$188K** | **$195K** | **$420K** | **$420K** | **$420K** | **$420K** | **$209K** |

**Updated:** 12 OCT 2016

## Goals/Milestones

**CY14 Goal** – Close study to enrolment and move lab to U of Arizona

☑ Completed move successfully. Funding transferred successfully

**CY15 Goals** – Complete preparations & launch study at UA

☑ Preparations, training, and MRI protocols successfully completed

☑ Study re-initiated in Arizona successfully!

☑ Preliminary findings published; several presentations submitted

**CY16-18 Goal** – Data collection, quality checks

☑ 37 Participants completed since relocation to UA; 68 participants have completed in total. Quarterly recruitment is ahead of schedule.

☐ Collect data from approximately 60 subjects per CY

**CY19 Goal** – Data analysis and dissemination

☐ Conduct final data analyses and prepare data for publication

**Comments/Challenges/Issues/Concerns**

- None. The study is progressing on target.

**Budget Expenditure to Date**

Cumulative Expenditure: $1,005,961

# DAY OF SCAN INFORMATION QUESTIONNAIRE

SUBJECT #:_____ DATE: ____/____/_____

---

AGE _____ years

HEIGHT _____ ft/inches

WEIGHT _____ lbs

SEX ☐ **MALE** ☐ **FEMALE**

For females only:

When was the start of your last menstrual period?

Be as precise as possible.

Date of period:_____

or about _____days ago.

RIGHT or LEFT-HANDED?

☐ **RIGHT**

☐ **LEFT**

☐ **BOTH/NEITHER**

Do you have any problems with reading? ☐ **NO** ☐ **YES**

**EDUCATION:** What is the highest grade or level of school you have completed or the highest degree you have obtained? *Please choose one:*

☐ 9th Grade
☐ 10th Grade
☐ 11th Grade
☐ 12th Grade, no diploma
☐ High school graduate
☐ GED or equivalent
☐ Some college, no degree
☐ Associate degree: occupational, technical, or vocational program
☐ Associate degree: academic program
☐ Bachelor's degree (e.g., BA, AB, BS, BBA)
☐ Master's degree (e.g., MA, MS, MEng, MEd, MBA)
☐ Professional school degree (e.g., MD, DDS, DVM, JD)
☐ Doctoral degree (e.g., PhD, EdD)
☐ Unknown

**RACE:** With what ethnicity do you identify?

☐ White
☐ Hispanic/Latino
☐ Black/African American
☐ Native American/ American Indian
☐ Asian/Pacific Islander
☐ Other

Are you currently doing shift work (e.g., working early morning, evening, or night shifts?

☐ **NO** ☐ **YES**

Do you engage in regular exercise?

☐ **NO** ☐ **YES**

Which sport? _____

How many days per week? _____

How many minutes per exercise session (on average)? _____

**CAFFEINE USE**

Did you have any caffeine containing products today?

☐ **NO** ☐ **YES** How much? _____

On average, how many cups (=8oz) of caffeinated coffee do you drink per day? _____

On average, how many cups (=8oz) of caffeinated tea do you drink per day? _____

On average, how many cans of caffeinated soda do you drink per day? _____

On average, how many caffeinated sports drinks do you drink per day? _____ (brand)

Do you use any other caffeinated products (e.g. Vivarin)?

☐ **NO** ☐ **YES** Brand? _____

How much? _____

How often? _____

**NICOTINE AND OTHER SUBSTANCE USE**

Do you currently smoke cigarettes?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever smoked cigarettes in the past?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently smoke large cigars?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly/ yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever smoked large cigars in the past?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently smoke small cigars?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly/ yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever smoked small cigars in the past?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently smoke cigarillos?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly/ yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever smoked cigarillos in the past?

☐ **NO** ☐ **YES**

How many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently use smokeless tobacco, such as dip or chew?

☐ **NO** ☐ **YES**

About how much/ many? _____daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever used smokeless tobacco in the past?

☐ **NO** ☐ **YES**

About how much/ many? _____ daily / weekly / monthly / yearly (*circle one*)

For how long? _____ years _____ months

When did you quit? _____ (approximate date)

Do you currently use any other nicotine-containing products?

☐ **NO** ☐ **YES**

Which kind? _____

For how long? _____ years _____ months

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Have you ever used any other kind of nicotine containing products?

☐ **NO** ☐ **YES**

Which kind? _____

For how long? _____ years _____ months

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

Have you tried to quit? ☐ **NO** ☐ **YES**

How many times? _____

Are you currently taking diet pills?

☐ **NO** ☐ **YES**

What brand? _____

For how long? _____ years _____ months _____ days

How much? _____

How often? _____ daily / weekly / monthly / yearly (*circle one*)

Are you currently taking any medications, vitamins, or supplements?

☐ **NO** ☐ **YES**

Please list:

Name: _____ Dosage: _____

Name: _____ Dosage: _____

Name: _____ Dosage: _____

Name: _____ Dosage: _____

Have you ever used any street drugs?

☐ **NO** ☐ **YES**

What? _____

How much? _____

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

In the past year, did you use any other street drugs?

☐ **NO**☐ **YES**

What? _____

How much? _____

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

Do you currently use any other street drugs?

☐ **NO** ☐ **YES**

What? _____

How much? _____

How often? _____daily/ weekly/ monthly/ yearly *(circle one)*

Do you drink alcohol?

☐ **NO** ☐ **YES**

How many times per month? _____

Using the below chart, what is the average number of drinks you consume on these occasions? _____

Using the chart, what is the largest number of drinks you consume? _____

One drink equals:

| 12 fl oz of **regular beer** | = | 8-9 fl oz of **malt liquor** (shown in a 12-oz glass) | = | 5 fl oz of **table wine** | = | 3-4 oz of **fortified wine** (such as sherry or port; 3.5 oz shown) | = | 2-3 oz of **cordial, liqueur, or aperitif** (2.5 oz shown) | = | 1.5 oz of **brandy** (a single jigger or shot) | = | 1.5 fl oz shot of **80-proof spirits** ("hard liquor") |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  | |  | |  | |  | |  | |  | |  |
| about 5% alcohol | | about 7% alcohol | | about 12% alcohol | | about 17% alcohol | | about 24% alcohol | | about 40% alcohol | | about 40% alcohol |

**INFORMATION ON THE MOST RECENT DOCUMENTED INJURY**

Injury date and time: __ __ _ /__ __/ __ __ __ __**:** __ __(24 hour clock)
(day /month/ year)

What happened? _____

_____

_____

Did you experience any symptoms or changes after the injury?

☐ **NO** ☐ **YES, IMMEDIATELY AFTER THE INJURY**

☐ **YES, NOT IMMEDIATELY AFTER THE INJURY**

Which symptoms or changes did you experience?

_____

_____

_____

At the time of the injury, were you under the influence of alcohol, medication or drugs at that time?

☐ **NO** ☐ **YES, ALCOHOL**

☐ **YES, MEDICATION** (which?) _____

☐ **YES, DRUGS** (which?) _____

Were medical services received after injury?

☐ **NO** ☐ **DO NOT KNOW** ☐ **YES**

Did you "see stars" during your last concussion?

☐ **NO** ☐ **DO NOT KNOW** ☐ **YES**

Did you experience loss of consciousness?

☐ **NO** ☐ **DO NOT KNOW** ☐ **YES**

Duration of loss of consciousness:

- ☐ <1 minute
- ☐ 1-29 minutes
- ☐ 30-59 minutes
- ☐ 1-24 hours
- ☐ 1-7 days
- ☐ > 7 days
- ☐ Unknown

How was the loss of consciousness verified?

☐ **Self-report** ☐ **Witness** ☐ **Medical chart**

Do you have a PERSONAL memory of the event/ incident itself?

☐ **YES, I FULLY REMEMBER** ☐ **YES, BUT THERE ARE GAPS IN MY MEMORY**

☐ **NO, I DO NOT REMEMBER AT ALL**

How much do you NOT remember after the injury?

- ☐ <1 minute
- ☐ 1-29 minutes
- ☐ 30-59 minutes
- ☐ 1-24 hours
- ☐ 1-7 days
- ☐ > 7 days
- ☐ Unknown

How was the memory loss verified?

☐ **Self-report** ☐ **Witness** ☐ **Medical chart**

After the injury, when did you feel back to yourself or 100%? Please state the approximate number of days. _____

How many separate injuries do you think have you sustained in total? _____

How many of these were documented by a health professional, athletic trainer, coach, etc.? _____

**SLEEP HABITS**

How much sleep did you get last night? _____ HRS

**Before** your injury, what time did you typically awaken on:

Weekdays (Mon-Fri)? _____ AM PM (midnight = 12 AM; noon = 12 PM)

Weekends (Sat-Sun)? _____ AM PM

**Before** your injury, how long did it typically take you to fall asleep at night?

Week nights (Sun-Thur) _____ MIN HRS (midnight = 12 AM; noon = 12 PM)

Weekends (Fri-Sat) _____ MIN HRS

**Before** your injury, at what time did you normally go to bed at night on:

Week nights (Sun-Thur)? _____ AM PM (midnight = 12 AM; noon = 12 PM)

Weekends (Fri-Sat)? _____ AM PM

**Before** the injury, did you experience sleep problems?

☐ **NO** ☐ **YES, I had trouble falling asleep.**

How often? _____ times per WEEK MONTH YEAR

☐ **YES, I had trouble staying asleep.**

How often? _____ times per WEEK MONTH YEAR

**Since the injury**, did you notice that your sleep became worse?

☐ **NO** ☐ **YES**

What sleep problems became more noticeable to you? (*check all that apply*)

☐ I get sleepier during the day.

☐ I get drowsier than I used to when trying to concentrate or work.

☐ I fall asleep when I should not.

☐ It is harder to stay alert during the day.

☐ It is harder to fall asleep at night.

How often? _____ times per WEEK MONTH YEAR *(circle one)*

☐ I fall asleep much later than I used to.

☐ I fall asleep much earlier than I used to.

☐ I sleep later in the morning than I used to.

☐ I have trouble staying asleep.

How often? _____ times per WEEK MONTH YEAR (circle one)

☐ I wake up much earlier in the morning than I used to.

☐ When I do sleep, it is fitful or less restful than it used to be.

☐ I wake up off and on throughout the night more than I used to.

☐ I have more nightmares than I used to.

**Since your injury,** how much do you typically sleep on weeknights (Sun-Thur)? _____ HRS

**Since your injury,** how much do you typically sleep on weekend nights (Fri-Sat)? _____ HRS

**Since your injury,** at what time do you normally go to bed at night on:

Week nights (Sun-Thur)? _____ AM PM (midnight = 12 AM; noon = 12 PM)

Weekends (Fri-Sat)? _____ AM PM

**Since your injury,** what time do you typically awaken on:

Weekdays (Mon-Fri)? _____ AM PM

Weekends (Sat-Sun)? _____ AM PM

**Since your Injury,** how long does it typically take you to fall asleep at night?

Week nights (Sun-Thur)? _____ MIN HRS

Weekends (Fri-Sat)? _____ MIN HRS

**Since your injury,**

at what time of day do you feel sleepiest? _____ AM PM

at what time of day do you feel most alert? _____ AM PM

how many hours do you need to sleep to feel your best? _____

if you get less than _____ hours of sleep, you notice impairment in your ability to function at work.

if you get more than _____ hours of sleep, you notice impairment in your ability to function at work.

**Since your injury**, do you take more than two daytime naps per month?

☐ **NO** ☐ **YES**

How many times per week do you nap? _____

At what time? ____:____ AM/PM to ____:____AM/PM

Do you consider yourself a light, normal, or heavy sleeper?

☐ **LIGHT** ☐ **NORMAL** ☐ **HEAVY**

Have you been told or do you think that you snore excessively?

☐ **NO** ☐ **YES**

Have you ever been diagnosed or treated for sleep apnea or sleep disordered breathing?

☐ **NO** ☐ **YES**

Is daytime sleepiness currently a problem for you?

☐ **NO** ☐ **YES**

**Epworth Sleepiness Scale**

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your **usual way of life in recent times**. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

| SITUATION | CHANCE OF DOZING | | | |
|---|---|---|---|---|
| Sitting and reading | **0** | **1** | **2** | **3** |
| Watching TV | **0** | **1** | **2** | **3** |
| Sitting, inactive in a public place (e.g. a theater or meeting) | **0** | **1** | **2** | **3** |
| As a passenger in a car for an hour without a break | **0** | **1** | **2** | **3** |
| Lying down to rest in the afternoon when circumstances permit | **0** | **1** | **2** | **3** |
| Sitting and talking to someone | **0** | **1** | **2** | **3** |
| Sitting quietly after a lunch without alcohol | **0** | **1** | **2** | **3** |
| In a car, while stopped for a few minutes in the traffic | **0** | **1** | **2** | **3** |

Subject ID: _____ Date: _____

Glasgow Outcome Scale – Extended

| | | | |
|---|---|---|---|
| **CONSCIOUSNESS** | | | |
| 1. | Is the subject able to obey simple commands, or say words? | NO | YES |
| **INDEPENDENCE IN THE HOME** | | | |
| 2.a | Is assistance of another person at home essential every day for some activities of daily living? | NO | YES |
| | Notes. | | |
| 2.b | Do you need frequent help or someone to be around at home most of the time? | NO<br>*(UPPER SD)* | YES<br>*(LOWER SD)* |
| 2.c | Was assistance at home essential before the injury? | NO | YES |
| | Notes. | | |
| **INDEPENDENCE OUTSIDE OF HOME** | | | |
| 3.a | Do you shop without assistance? | NO<br>*(UPPER SD)* | YES |
| 3.b | Did you need assistance before the injury? | NO | YES |
| | Notes. | | |
| 4.a | Do you travel without assistance? | NO<br>*(UPPER SD)* | YES |
| 4.b | Did you need assistance before the injury? | NO | YES |
| | Notes. | | |

Subject ID: _____ Date: _____

| | | | | |
|---|---|---|---|---|
| **WORK** | | | | |
| 5.a | Are you currently working to your previous capacity? | NO | | YES |
| 5.b | How restricted are you? | Reduced work capacity.<br><br>(UPPER MD) | | Able to work in sheltered workshop or non-competitive job, or unable to work<br><br>(LOWER MD) |
| 5.c | Have you been working or seeking employment before the injury? | NO | | YES |
| | Notes. | | | |
| **SOCIAL & LEISURE ACTIVITIES** | | | | |
| 6.a | Are you able to resume regular social and leisure activities outside home? | NO | | YES |
| 6.b | What is the extent of the restriction? | Participate a bit less: at least half as often as before injury<br><br>(LOWER GR) | Participate much less: less than half as often<br><br>(UPPER MD) | Unable to participate: rarely, if ever<br><br>(LOWER MD) |
| 6.c | Did you engage in regular social and leisure activities before the injury? | NO | | YES |
| | Notes. | | | |
| **FAMILY & FRIENDSHIPS** | | | | |
| 7.a | Have there been any psychological problems which have resulted in ongoing family disruption or disruption of friendship? | NO | | YES |

Subject ID: _____ Date: _____

| | | | | |
|---|---|---|---|---|
| 7.b | What is the extent of disruption or strain? | Occasional: less than weekly | Frequent: once a week or more, but tolerable | Constant: daily and intolerable |
| 7.c | Were there problems with family or friends before the injury? | NO | YES | |
| | Notes. | | | |
| **RETURN TO NORMAL LIFE** | | | | |
| 8.a | Are there any other current problems relating to the injury which affect daily life? | NO<br><br>(UPPER GR) | YES<br><br>(LOWER GR) | |
| 8.b | Were similar problems present before injury? | NO | YES | |
| | Notes. | | | |

| **SCORING** | | |
|---|---|---|
| 1 | Dead | |
| 2 | Vegetative State | VS |
| 3 | Lower Severe Disability | Lower SD |
| 4 | Upper Severe Disability | Upper SD |
| 5 | Lower Moderate Disability | Lower MD |
| 6 | Upper Moderate Disability | Upper MD |
| 7 | Lower Good Recovery | Lower GR |
| 8 | Upper Good Recovery | Upper GR |

CD-RISC

Subject #: Date: _____ Time: _____

_____

Think about how you have been feeling over the past month. Using the scale below, please rate each of the following statements for how well they describe you **DURING THE PAST MONTH**.

| **0** | **1** | **2** | **3** | **4** |
|---|---|---|---|---|
| **not true at all** | **rarely true** | **sometimes true** | **often true** | **true nearly all the time** |

1. _____ Able to adapt to change
2. _____ Close and secure relationships
3. _____ Sometimes fate or God can help
4. _____ Can deal with whatever comes
5. _____ Past success gives confidence for new challenge
6. _____ See the humorous side of things
7. _____ Coping with stress strengthens
8. _____ Tend to bounce back after illness or hardship
9. _____ Things happen for a reason
10. _____ Best effort no matter what
11. _____ You can achieve your goals
12. _____ When things look hopeless, I don't give up
13. _____ Know where to turn for help
14. _____ Under pressure, focus and think clearly
15. _____ Prefer to take the lead in problem solving
16. _____ Not easily discouraged by failure
17. _____ Think of self as strong person
18. _____ Make unpopular or difficult decisions
19. _____ Can handle unpleasant feelings
20. _____ Have to act on a hunch
21. _____ Strong sense of purpose
22. _____ In control of your life
23. _____ I like challenges
24. _____ You work to attain your goals
25. _____ Pride in your achievements

# Craig Handicap Assessment and Reporting Technique Scoring Short Form

1. How many hours in a typical 24-hour day do you have someone with you to provide physical assistance for personal care activities such as eating, bathing, dressing, toileting and mobility?

_____ hours paid assistance _____ hours unpaid (family, others)

**PHYSICAL INDEPENDENCE**

A. Total the hours of paid and unpaid care, multiply by 4, and subtract that number from 100.

100
minus
_____.
=

| |
|---|
| |

2. How much time is someone with you in your home to assist you with activities that require remembering, decision making, or judgment?

1_____ Someone else is always with me to observe or supervise.
2_____ Someone else is always around, but they only check on me now and then.
3_____ Sometimes I am left alone for an hour or two.
4_____ Sometimes I am left alone for most of the day
5_____ I have been left alone all day and all night, but someone checks in on me.
6_____ I am left alone without anyone checking on me.

3. How much of the time is someone with you to help you with remembering, decision making, or judgment when you go away from your home?

1_____ I am restricted from leaving, even with someone else.
2_____ Someone is always with me to help with remembering, decision making or judgment when I go anywhere.
3_____ I go to places on my own as long as they are familiar.
4_____ I do not need help going anywhere.

**COGNITIVE INDEPENDENCE**

A. Assign points as follows: response #1 = 0 points; response #2 = 1 point; response #3 = 2 points; response #4 = 3 points; response #5 = 4 points; and response #6 = 5 points.

_____.
x11
=
_____.

B. Multiply points in "A" by 11.

+

C. Assign points as follows: response #1 = 0 points; response #2 = 1 point; response #3 = 2 points; and response #4 = 3 points.

_____.
x15
=
_____.

D. Multiply points in "C" by 15.

=

Add the sums of "B" and "D". If the total sum is greater than 100, enter 100.

| |
|---|
| |

4. On a typical day, how many hours are you out of bed? _____ hours

5. In a typical week, how many days do you get out of your house and go somewhere? _____days

6. In the last year, how many nights have you spent away from your home (excluding hospitalizations?)
_____ none _____ 1-2 _____ 3-4 _____ 5 or more

**MOBILITY**

A. Multiply the number of hours out of bed by 3. _____.

\+

B. Multiply the number of days per week out of the house by 7. _____.

\+

C. Assign points as follows: no nights out = 0; 1-2 nights out = 10; 3-4 nights out = 15; 5 or more nights = 20. If the total sum is greater than 100, enter 100. _____.

=

Add the sums of "A", "B", and "C". If the total sum is greater than 100, enter 100. [ ]

7. How many hours per week do you spend working in a job for which you get paid? hours_____

8. How many hours per week do you spend in school working toward a degree or in an accredited technical training program (including hours in class and studying)? hours

9. How many hours per week do you spend in active homemaking including parenting, housekeeping, and food preparation? _____ hours

10. How many hours per week do you spend in home maintenance activities such as gardening, house repairs or home improvement? _____ hours

11. How many hours per week do you spend in recreational activities such as sports, exercise, playing cards, or going to movies? Please do not include time spent watching TV or listening to the radio._____hours

**OCCUPATION**

A. Multiply the number of hours working by 2.5. _____.

\+

B. Multiply the number of hours in school by 2.5. _____.

\+

C. Multiply the number of hours in active homemaking by 2.5. _____.

\+

D. Multiply the number of hours in home maintenance by 2.5. _____.

\+

E. Multiply the number of recreational activities by 1.25 _____.

=

Add the sums of "A", "B", "C", "D", and "E". If the total sum is greater than 100, enter 100. [ ]

**SOCIAL INTEGRATION**

12. How many people do you live with?

**13. Is one of them your spouse or significant other?**

**14. of the people you live with how many are relatives?**

15. How many business or organizational associates do you visit, phone, or write to at least once a month? _____ Associates

16. How many friends (non-relatives contacted outside business or organizational settings) do you visit, phone, or write to at least once a month?_____Friends

17. With how many strangers have you initiated a conversation in the last month (for example, to ask information or place an order)?

    none ____ 1-2 ____ 3-5 ____ 6 or more

A. Assign 38 points if living with spouse/partner OR assign 25 points if living with unrelated roommate and/or an attendant.

   Add an additional six points for every relative that lives in the household.

_____.
+

B. Multiply number of business associates by 2.5. A maximum score for this component is 25 points.

_____.
+

C. If living with more than one roommate, add extra roommate to number of friends contacted monthly. Multiply by 13. A Maximum score for this component is 65 points.

_____.
+

D. Assign points as follows: none = 0 points; 1-2 = 15 points; 3-5 = 23 points; 6 or more = 30 points.

_____.

=

Add the sums from "A", "B", "C", and "D". If the total sum is greater than 100, enter 100.

| |
|---|
| |

18. Approximately what was the combined annual income, in the last year, of **all family members in your household**? (consider all sources including wages and earnings, disability benefits, pensions and retirement income, income from court settlements, investments and trust funds, child support and alimony, contributions from relatives, and any other source.)

a. Less than 25,000 - If no ask e; if yes ask b
b. Less than 20,000 - If no code 22500; if yes ask c
c. Less than 15,000 - If no code 17500; if yes ask d
d. Less than 10,000 - If no code 12500; if yes code 5000
e. Less than 35,000 - If no ask f; if yes code 30000
f. Less than 50,000 - If no ask g; if yes code 42500
g. Less than 75,000 - If no code h; if yes code 62500
h. 75,000 or more code 80000

19. Approximately how much did you pay last year for medical care expenses? (Consider any amounts paid by yourself or the family members in your household and **not reimbursed** by insurance or benefits.)

a. Less than 1000 if "no" ask b if "yes" code 500.
b. Less than 2500 if "no" ask c if "yes" code 1750.
c. Less than 5000 if "no" ask d if "yes" code 3750.
d. Less than 10000 if "no" code e if "yes" code 7500.
e. 10000 or more code 15000

**ECONOMIC SELF SUFFICIENCY**

A. Calculate family size by adding respondent, plus partner (if living with respondent), plus other relatives in household.

_____.
Family size

_____.
(#19)
minus

B. Subtract the unreimbursed medical expenses from the annual income (amount in question #19 minus amount in question #20.

_____.
(#20)

C. Determine poverty level from family size calculated in "A".

=

D. Divide the value from "B" by the poverty level from "C".

_____.
divided by

E. Multiply by 50

_____.
Poverty level

*50
=

_____.

=

If the total sum is greater than 100, enter 100.

| |
|---|
| |

# Personality Assessment Inventory (PAI)



## Personality Assessment Inventory™ (PAI®)

**Leslie C. Morey, PhD**


Revised and updated materials help increase the accuracy of personality assessment.

**Purpose:** 22 nonoverlapping full scales provide a comprehensive assessment of adult psychopathology in ages 18 years and older

**Age Range:** Adult
Elder Adult

**Admin:** Individual or group

**Time:** 50-60 minutes to administer; 15-20 minutes to score

**Qualification:** C

**Sample Reports:** N/A

**Related Products:** PAI® Professional Report Service

PAI® Software Portfolio

Personality Assessment Inventory™-Adolescent

With its newly revised Professional Manual, Profile Form Adults-Revised, and Critical Items Form-Revised, the PAI® continues to raise the standard for the assessment of adult psychopathology. This objective inventory of adult personality assesses psychopathological syndromes and provides information relevant for clinical diagnosis, treatment planning, and screening for psychopathology. Since its introduction, the PAI has been heralded as one of the most important innovations in the field of clinical assessment.

### PAI® Scales and Subscales

The 344 PAI items constitute 22 nonoverlapping scales covering the constructs most relevant to a broad-based assessment of mental disorders: 4 validity scales, 11 clinical scales, 5 treatment scales, and 2 interpersonal scales. To facilitate interpretation and to cover the full range of complex clinical constructs, 10 scales contain conceptually derived subscales.

The PAI Clinical scales were developed to provide information about critical diagnostic features of 11 important clinical constructs. These 11 scales may be divided into three broad classes of disorders: those within the neurotic spectrum, those within the psychotic spectrum, and those associated with behavior disorder or impulse control problems.

The Treatment scales were developed to provide indicators of potential complications in treatment that would not necessarily be apparent from diagnostic information. These five scales include two indicators of potential for harm to self or others, two measures of the respondent's environmental circumstances, and one indicator of the respondent's motivation for treatment.

The Interpersonal scales were developed to provide an assessment of the respondent's interpersonal style along two dimensions: a warmly affiliative versus a cold rejecting style, and a dominating/controlling versus a meekly submissive style. These axes provide a useful way of conceptualizing many different mental disorders: persons at the extremes of these dimensions may present with a variety of disorders. A number of studies provide evidence that diagnostic groups differ on these dimensions.

The PAI includes a Borderline Features scale and an Antisocial Features scale. Both of these scales specifically assess character pathology. The Borderline Features scale is the only PAI scale that has four subscales, reflecting the factorial complexity of the construct. The Antisocial Features scale includes a total of three facets: one assessing antisocial behaviors, and the other two assessing antisocial traits.

Subject ID: _____ Date: _____

The following questions concern your alcohol consumption. Place an X in one box that best describes your answer to each question.

| Questions | 0 | 1 | 2 | 3 | 4 | |
|---|---|---|---|---|---|---|
| 1. How often do you have a drink containing alcohol? | Never | Monthly or less | 2-4 times a month | 2-3 times a week | 4 or more times a week | |
| 2. How many drinks containing alcohol do you have on a typical day when you are drinking? | 1 or 2 | 3 or 4 | 5 or 6 | 7 to 9 | 10 or more | |
| 3. How often do you have six or more drinks on one occasion? | Never | Less than monthly | Monthly | Weekly | Daily or almost daily | |
| 4. How often during the last year have you found that you were not able to stop drinking once you had started? | Never | Less than monthly | Monthly | Weekly | Daily or almost daily | |
| 5. How often during the last year have you failed to do what was normally expected of you because of drinking? | Never | Less than monthly | Monthly | Weekly | Daily or almost daily | |
| 6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? | Never | Less than monthly | Monthly | Weekly | Daily or almost daily | |
| 7. How often during the last year have you had a feeling of guilt or remorse after drinking? | Never | Less than monthly | Monthly | Weekly | Daily or almost daily | |
| 8. How often during the last year have you been unable to remember what happened the night before because of your drinking? | Never | Less than monthly | Monthly | Weekly | Daily or almost daily | |
| 9. Have you or someone else been injured because of your drinking? | No | | Yes, but not in the last year | | Yes, during the last year | |
| 10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down? | No | | Yes, but not in the last year | | Yes, during the last year | |
| | | | | | **Total** | |

# Rivermead Post Concussion Symptoms Questionnaire

Modified (Rpq-3 And Rpq-13)[42] Printed With Permission: Modified Scoring System From Eyres 2005 [28]

Subject ID: Date:

After a head injury or accident some people experience symptoms that can cause worry or nuisance. We would like to know if you now suffer any of the symptoms given below. Because many of these symptoms occur normally, we would like you to compare yourself now with before the accident. For each symptom listed below please circle the number that most closely represents your answer.

0 = not experienced at all
1 = no more of a problem
2 = a mild problem
3 = a moderate problem
4 = a severe problem

Compared with **before** the accident, do you **now** (i.e., over the last 24 hours) suffer from:

| | not experienced | no more of a problem | mild problem | moderate problem | severe problem |
|---|---|---|---|---|---|
| Headaches | 0 | 1 | 2 | 3 | 4 |
| Feelings of dizziness | 0 | 1 | 2 | 3 | 4 |
| Nausea and/or vomiting | 0 | 1 | 2 | 3 | 4 |
| | | | | | |
| Noise sensitivity (easily upset by loud noise) | 0 | 1 | 2 | 3 | 4 |
| Sleep disturbance | 0 | 1 | 2 | 3 | 4 |
| Fatigue, tiring more easily | 0 | 1 | 2 | 3 | 4 |
| Being irritable, easily angered | 0 | 1 | 2 | 3 | 4 |
| Feeling depressed or tearful | 0 | 1 | 2 | 3 | 4 |
| Feeling frustrated or impatient | 0 | 1 | 2 | 3 | 4 |
| Forgetfulness, poor memory | 0 | 1 | 2 | 3 | 4 |
| Poor concentration | 0 | 1 | 2 | 3 | 4 |
| Taking longer to think | 0 | 1 | 2 | 3 | 4 |
| Blurred vision | 0 | 1 | 2 | 3 | 4 |
| Light sensitivity (easily upset by bright light) | 0 | 1 | 2 | 3 | 4 |
| Double vision | 0 | 1 | 2 | 3 | 4 |
| Restlessness | 0 | 1 | 2 | 3 | 4 |
| | | | | | |
| Are you experiencing any other difficulties? Please specify, and rate as above. | | | | | |
| 1. | 0 | 1 | 2 | 3 | 4 |
| 2. | 0 | 1 | 2 | 3 | 4 |

*Administration only:*

| | |
|---|---|
| ***RPQ-3*** *(total for first three items)* | |
| ***RPQ-13*** *(total for next 13 items)* | |

http://www.maa.nsw.gov.au/default.aspx?MenuID=148

# Rivermead Post Concussion Symptoms Questionnaire (cont.)

Modified (Rpq-3 And Rpq-13)[42] Printed With Permission: Modified Scoring System From Eyres 2005 [28]

**Administration only**

Individual item scores reflect the presence and severity of post concussive symptoms. Post concussive symptoms, as measured by the RPQ, may arise for different reasons subsequent to (although not necessarily directly because of) a traumatic brain injury. The symptoms overlap with broader conditions, such as pain, fatigue and mental health conditions such as depression[72].

The questionnaire can be repeated to monitor a patient's progress over time. There may be changes in the severity of symptoms, or the range of symptoms. Typical recovery is reflected in a reduction of symptoms and their severity within three months.

**Scoring**

The scoring system has been modified from Eyres, 2005[24].

The items are scored in two groups. The first group (RPQ-3) consists of the first three items (headaches, feelings of dizziness and nausea) and the second group (RPQ-13) comprises the next 13 items. The total score for RPQ-3 items is potentially 0–12 and is associated with early symptom clusters of post concussive symptoms. If there is a higher score on the RPQ-3, earlier reassessment and closer monitoring is recommended.

The RPQ-13 score is potentially 0–52, where higher scores reflect greater severity of post concussive symptoms. The RPQ-13 items are associated with a later cluster of symptoms, although the RPQ-3 symptoms of headaches, dizziness and nausea may also be present. The later cluster of symptoms is associated with having a greater impact on participation, psychosocial functioning and lifestyle. Symptoms are likely to resolve within three months. A gradual resumption of usual activities is recommended during this period, appropriate to symptoms. If the symptoms do not resolve within three months, consideration of referral for specialist assessment or treatment services is recommended.

**References:**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King, N. S., Crawford, S., Wenden, F.J., Moss, N.E.G. Wade, D.T. (1995). The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability *Journal of Neurology*, 242, 587-592.

Potter, S., Leigh, E., Wade, D., Fleminger, S. (2006). The Rivermead Post Concussion Symptoms Questionnaire *Journal of Neurology*, October 1-12.

Subject ID: _____ Session: _____ Study: _____ Date: ____/____/____

# Snaith-Hamilton Pleasure Scale

This questionnaire is designed to measure your ability to experience pleasure in the last few days.
It is important to read each statement very carefully.
Circle the answer that corresponds to how much you agree or disagree with each statement.

| | | | | | |
|---|---|---|---|---|---|
| 1. | I would enjoy my favorite television or radio program. ..... | Strongly Disagree | Disagree | Agree | Strongly Agree |
| 2. | I would enjoy being with my family or close friends. ..... | Definitely Agree | Agree | Disagree | Strongly Disagree |
| 3. | I would find pleasure in my hobbies and past-times. ..... | Strongly Disagree | Disagree | Agree | Strongly Agree |
| 4. | I would be able to enjoy my favorite meal. ..... | Definitely Agree | Agree | Disagree | Strongly Disagree |
| 5. | I would enjoy a warm bath or refreshing shower. ..... | Definitely Agree | Agree | Disagree | Strongly Disagree |
| 6. | I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread. ..... | Strongly Disagree | Disagree | Agree | Strongly Agree |
| 7. | I would enjoy seeing other people's smiling faces. ..... | Definitely Agree | Agree | Disagree | Strongly Disagree |
| 8. | I would enjoy looking smart when I have made an effort with my appearance. ..... | Strongly Disagree | Disagree | Agree | Strongly Agree |
| 9. | I would enjoy reading a book, magazine, or newspaper. ..... | Definitely Agree | Agree | Disagree | Strongly Disagree |
| 10. | I would enjoy a cup of tea or coffee or my favorite drink. ..... | Strongly Disagree | Disagree | Agree | Strongly Agree |
| 11. | I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend. ..... | Strongly Disagree | Disagree | Agree | Strongly Agree |
| 12. | I would be able to enjoy a beautiful landscape or view. ..... | Definitely Agree | Agree | Disagree | Strongly Disagree |
| 13. | I would get pleasure from helping others. ..... | Strongly Disagree | Disagree | Agree | Strongly Agree |
| 14. | I would feel pleasure when I receive praise from other people. .... | Definitely Agree | Agree | Disagree | Strongly Disagree |

**Satisfaction with Life Scale**

Below are five statements with which you may agree or disagree.
Indicate your agreement with each item by placing the appropriate number on the line preceding that item.

Please be open and honest in your responding.

The 7-point scale is as follows:

1 = strongly disagree
2 = disagree
3 = slightly disagree
4 = neither agree nor disagree
5 = slightly agree
6 = agree
7 = strongly agree

__ 1. In most ways my life is close to my ideal.
__ 2. The conditions of my life are excellent.
__ 3. I am satisfied with my life.
__ 4. So far I have gotten the important things I want in life.
__ 5. If I could live my life over, I would change almost nothing.

# EDINBURGH HANDEDNESS SURVEY

Subject ID#:_____

Date: _____

Please indicate your preferences in the use of hands in the following activities by putting a + in the appropriate column. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, put ++. If in any case you are really indifference put + in both columns.

Some of the activities require both hands. In these cases the part of the task, or object, for which the hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

---

| | | LEFT | RIGHT |
|---|---|---|---|
| 1 | Writing | | |
| 2 | Drawing | | |
| 3 | Throwing | | |
| 4 | Scissors | | |
| 5 | Toothbrush | | |
| 6 | Knife [without fork] | | |
| 7 | Spoon | | |
| 8 | Broom [upper hand] | | |
| 9 | Striking Match [match] | | |
| 10 | Opening Box [lid] | | |

---

Do not write below this line

L.Q.:_____ DECILE: _____

# M/USE QUESTIONNAIRE

SUBJECT #:_____ DATE: ____/____/_____

---

Have you ever used marijuana?

*For our purposes, marijuana usage is considered any instance in which you intentionally consumed (smoked, ingested, etc.) any quantity of marijuana.*

☐ **NO** ☐ **YES**

At what age did you start? _____

At what specific age (in years) was your marijuana usage the heaviest? _____

During your lifetime, approximately how many occasions have you used marijuana?

☐ 0-50 ☐ 51-100 ☐ 101-500 ☐ 501s-1000 ☐ 1001-5000 ☐ over 5000

Consider the extent of marijuana use throughout your lifetime. Please approximate the number of times per month on average which you used marijuana at the following ages:

| 16-18 years of age | 19-21 years of age | 22-24 years of age | 25-27 years of age | 28-30 years of age | 30+ years of age |
|---|---|---|---|---|---|
| | | | | | |

During your lifetime, on average, how many times per month have you used marijuana?

_____

In the past <u>four weeks</u>, did you use marijuana?

☐ **NO** ☐ **YES**

How often? _____ daily / weekly (*circle one*)

On average, how much do you consume per occasion? _____

**If YES**, please review the printed calendar reflecting all the days in the past month. Indicate the number of times you used marijuana on each of these days. If you abstained from marijuana use during a given day, please write a “0” on that day. Please fill out every day in the calendar with your best guess of marijuana use.

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Research paper

# Gray matter volume and executive functioning correlate with time since injury following mild traumatic brain injury

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## HIGHLIGHTS

- A voxel based morphometric study in people with mild traumatic brain injury.
- Longer duration of time since injury was associated with larger gray matter volume.
- Particularly in ventromedial prefrontal cortex and fusiform gyrus regions.
- Compensatory remodeling of cortical regions might be the reason for these findings.

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## ABSTRACT

Most people who sustain a mild traumatic brain injury (mTBI) will recover to baseline functioning within a period of several days to weeks. A substantial minority of patients, however, will show persistent symptoms and mild cognitive complaints for much longer. To more clearly delineate how the duration of time since injury (TSI) is associated with neuroplastic cortical volume changes and cognitive recovery, we employed voxel-based morphometry (VBM) and select neuropsychological measures in a cross-sectional sample of 26 patients with mTBI assessed at either two-weeks, one-month, three-months, six-months, or one-year post injury, and a sample of 12 healthy controls. Longer duration of TSI was associated with larger gray matter volume (GMV) within the ventromedial prefrontal cortex (vmPFC) and right fusiform gyrus, and better neurocognitive performance on measures of visuospatial design fluency and emotional functioning. In particular, volume within the vmPFC was positively correlated with design fluency and negatively correlated with symptoms of anxiety, whereas GMV of the fusiform gyrus was associated with greater design fluency and sustained visual psychomotor vigilance performance. Moreover, the larger GMV seen among the more chronic individuals was significantly greater than healthy controls, suggesting possible enlargement of these regions with time since injury. These findings are interpreted in light of burgeoning evidence suggesting that cortical regions often exhibit structural changes following experience or practice, and suggest that with greater time since an mTBI, the brain displays compensatory remodeling of cortical regions involved in emotional regulation, which may reduce distractibility during attention demanding visuo-motor tasks.



## 1. Introduction

Traumatic brain injury (TBI) affects approximately 1.5 million individuals each year [27]. While TBI can be classified as mild, moderate, or severe, the vast majority of these injuries are in the mild range [33]. In contrast to moderate or severe TBI, mild traumatic brain injury (mTBI) is diagnosed following a blow or other insult to the head that leads to transient alterations in cognitive, sensory, or motor functioning, and may or may not involve brief loss of consciousness (i.e., no more than 30 min), and is usually not associated with identifiable abnormalities on standard clinical neuroimaging [2]. Common post-concussive symptoms include reduced attention, memory, and information processing speed [4,21]. Psychiatric

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0304-3940/

mood disturbances, including anxiety, depression, post-traumatic stress, and phobic symptoms, are often elevated among those with mTBI compared to healthy controls [3]. For most individuals who have sustained an mTBI, the associated cognitive and affective symptoms reduce with longer time since injury (TSI), typically resolving to baseline levels within the first few days or weeks post-injury [21] and full recovery within 90 days [14]. However, some evidence suggests that nearly 50% of patients with mTBI show some persistent deficits at three months [26], and a smaller proportion will continue to have chronic post-concussive symptoms or cognitive deficits that persist for at least a year or longer [29]. Despite the rapid advancement of powerful neuroimaging techniques, little is known about the structural brain changes that are associated with the recovery process.

Voxel-based morphometry (VBM) is a neuroimaging technique that enables quantification of regional gray matter volume (GMV) throughout the cortex. A number of studies suggest that GMV may be reduced in patients with mTBI compared to healthy controls in the semi-acute to post-acute stages [12,19]. Others have shown that GMV often remains decreased in various areas of the cortex when assessed for up to a year after injury [11,39]. The research to date, however, has not examined whether and how GMV differs at various time-points following an injury nor investigated whether there are regions of increased GMV with longer recovery time, and whether this correlates with possible recovery of cognitive capacities. This latter question is important, as numerous studies have suggested that regional GMV can be increased through training or practice in particular cognitive and motor domains [20,32]. This remodeling process is known as experience-dependent cortical plasticity [15], and involves increases in dendritic arborization or neuronal spine density as a result of frequent neuronal stimulation or use (i.e., practice) [5,16]. This raises the possibility that individuals who repeatedly engage in particular cognitive or emotional strategies to compensate for their deficits might show increased experience-dependent cortical remodeling of relevant cortical structures, which over time, might be expressed as increased GMV within those structures.

The goal of the present study was to examine regional GMV within individuals following mTBI at various time-points post-injury and correlate GMV with neuropsychological and emotional functioning. Based on the aforementioned rationale of compensation through experience-dependent cortical plasticity, we hypothesized that greater TSI would be associated with increased GMV within prefrontal regions involved in regulating attention, emotion, and behavior (e.g., dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial/ventromedial prefrontal cortex), and that greater volume in such regions would correlate with better speed of information processing, greater vigilance, and reduced neuropsychiatric symptom expression.

## 2. Methods

### 2.1. Participants

Twenty-six right-handed, native English speaking, individuals (age range 20–45 years, mean age 23.38 ± 5.23, 11 males, 15 females) with a history of mTBI experienced within the preceding 12 months took part in this study (two-weeks [$n = 2$], one-month [$n = 6$], three-months [$n = 5$], six-months [$n = 10$], one-year [$n = 3$]). All participants were recruited from the Boston metropolitan area using advertisements on the Internet, public transportation billboards, newspaper, radio, and posted flyers. Eligible participants were required to have sustained a documented injury involving head impact, followed by some alteration in mental status (e.g., confusion, “seeing stars”, disorientation, post-traumatic amnesia not more than 24 h) or loss of consciousness lasting no more than 30 min. To be eligible, participants had to provide written documentation from an impartial but professionally responsible witness to the head injury (e.g., coach, sports trainer, police officer) or its immediate medical aftermath (e.g., physician, nurse, ambulance driver, medical record, neuropsychologist). In addition, 12 healthy control participants (age range 20–43 years, mean age 25.00 ± 6.55, 4 males, 8 females), without history of head injury or loss of consciousness were also recruited for comparison. Participants were compensated for their time. All study procedures were conducted in accordance with the 1964 declaration of Helsinki and were approved by the McLean Hospital Institutional Review Board. Furthermore, because the study was funded by the US Army Medical Research and Materiel Command (USMRMC), all procedures were also approved by the US Army Human Research Protections Office.

### 2.2. Materials and procedure

Based on the timing of their injury, mTBI participants were scheduled for an evaluation at one of six different time-points following their mTBI: 2-weeks, 1-month, 3-months, 6-months, or 12-months post injury (all sessions were scheduled within 3 days of the respective anniversary date). Participants underwent a morning assessment session that involved completing several questionnaires and cognitive tasks, followed by a series of neuroimaging scans. Healthy control participants underwent the same structural scanning sequence.

### 2.3. Neuropsychological assessments

#### 2.3.1. Delis–Kaplan Executive Function System (D–KEFS)

Participants with mTBI were administered the Delis–Kaplan Executive Function System (D–KEFS), a widely used metric of higher order executive functions with established psychometric properties [6,34]. The D–KEFS provides methods for delineating underlying cognitive processes that may contribute to executive functioning. For the present analyses, we focused on two ‘matched fluency’ subtasks of the D–KEFS, (1) the verbal fluency (VF) subtest to measure verbally mediated executive control, and (2) the Design Fluency (DF) subtest to measure visuospatial executive control. For VF, four subtests were collected, including VF1 (letter fluency: number of items correct), VF2 (category fluency: number of items correct), VF3 (switching: number of items correct regardless of whether switching rule was correct), and VF3-A (switching accuracy: number of correct category switches). VF1 required the examinee to say as many words that they could think of in 60 s that began with a particular letter. VF2 required the examinee to name as many animals that they could think of in 60 s. VF3 required the examinee to name as many fruits and furniture as possible in 60 s, alternating between categories for each item. VF3-A is derived from the number of correct across-category switches from the VF3 trial. This procedure allows determination of whether deficits are due to more fundamental executive processes (VF1 and VF2) or higher level executive processes involved in switching (VF3 and VF3-A). For DF, a task that requires the examinee to connect pre-printed circles together using straight lines to make as many uniquely different designs as possible in 60 s, the following three related subtests were evaluated: DF1 (filled dots: number of correctly connected black circles), DF2 (empty dots: number of correctly connected empty circles), and DF3 (switching: number of correct designs where the examinee alternated between filled and empty circles). DF1 required the examinee to generate as many different designs as possible by connecting sets comprised of filled black circles using only 4 straight lines per design. DF2 is nearly identical to DF1, except that the pre-printed sets include both empty and filled circles, requiring the examinee to inhibit the prepotent response

from the previous trial (i.e., connecting filled circles). DF3 required the examinee to create designs such that each line has a filled circle at one end point and an empty circle at the other.

#### 2.3.2. Psychomotor vigilance test (PVT)

Participants with mTBI were administered a 10-min version of the psychomotor vigilance test (PVT), a well-validated metric for the assessment of sustained vigilance and response time [9]. During this computerized task, participants pressed a response key as quickly as possible each time a pseudo-randomly presented stimulus (time interval ranged from 2 to 10 s) appeared on the screen. For the present study, mean simple reaction time derived from the entire duration of the task was used as the metric of interest.

#### 2.3.3. Wechsler abbreviated scale of intelligence (WASI-II)

All participants were also administered the Wechsler Abbreviated Scale of Intelligence (WASI-II) [36] by a trained research technician to provide an estimate of general cognitive ability. For this study, the full-scale intelligence quotient (FSIQ) was calculated from the four-subtest version of the WASI-II.

#### 2.3.4. Personality assessment inventory (PAI)

Finally, as in index of potential clinical anxiety problems, mTBI participants also completed the anxiety related disorders (ARD) scale of the Personality Assessment Inventory (PAI) [22]. This scale measures the general behavioral expression of anxiety and maladaptive attempts to control anxiety, particularly as they relate to intrusive thoughts, common phobic fears, and prior traumatic experiences. For the present analysis, normalized *T*-scores based on the standard community sample were used [22].

### 2.4. Magnetic resonance imaging parameters

#### 2.4.1. Data acquisition

A 3.0 T magnetic resonance imaging scanner (Siemens Tim Trio, Erlangen, Germany) with a 32-channel head coil was used for the study. For this analysis, a T-1 weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s, 2.3 ms, 12°) was used to obtain 176 sagittal slices (256 × 256 matrix) with a slice thickness of 1 mm and a voxel size of 1 × 1 × 1 mm. Participants also completed several other neuroimaging sequences, including diffusion tensor imaging and a resting state functional scan, but these were not relevant to the present analysis and will not be discussed further.

#### 2.4.2. Voxel based morphometry (VBM) image processing

T-1 weighted structural images were preprocessed using the VBM8 toolbox in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Images were realigned to the anterior–posterior commissure axis in SPM8. After realignment, images were segmented into gray matter, white matter, and cerebrospinal fluid using VBM8, a fully automated algorithm in SPM8. Segmented images were used to create a custom DARTEL template and then the images were normalized to Montreal Neurological institute (MNI) space. Smoothing of normalized images was performed with a 10 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

### 2.5. Statistical analysis

Statistical analyses were conducted in two stages. First, GMV was regressed against days since injury. In this stage, the normalized, smoothed gray matter images were entered into a whole-brain general linear model (GLM) in SPM8. We used a cluster-extent based thresholding, following the recommended approach suggested by Woo, Krishnan, and Wager [38], applying a primary significance threshold of $p < 0.001$, uncorrected, as the default lower limit. Based on this primary height threshold, SPM12 provided the critical cluster size for cluster-extent correction with false discovery rate (FDR) maintained at $p < 0.05$. Based on the present data, this threshold was k = 894 voxels. Additionally, age, gender, and intracranial volume (ICV) were included as nuisance covariates in the regression equation.

In the second stage of analysis, estimates of GMV were extracted for each distinct cluster exceeding our significance threshold. For this analysis, the total cluster eigenvariate was extracted for each participant and then exported into IBM SPSS Statistics 22 for correlational analysis with neuropsychological test scores. It was predicted that GMV would correlate positively with better neuropsychological performance among the patients with mTBI. Partial correlations between GMV of each regional cluster and neuropsychological scores were calculated, controlling for FSIQ and education level ($\alpha = 0.05$, 1-tailed). For the ARD, analyses were also controlled for the positive and negative impression validity index scores.

Finally, the GMV findings for the mTBI sample were compared to a group of 12 healthy control participants to determine if the changes in GMV over time differed from the normal pattern in non-injured individuals. For this analysis, the mTBI sample was divided into the "post-acute" stage (i.e., 0–99 days post injury; $n = 13$) and the chronic stage (i.e., 100–367 days post injury; $n = 13$), and compared to a third group of healthy controls ($n = 12$) using a one-way analysis of variance in SPM12, with age, sex, and ICV entered as nuisance covariates. Contrast estimates were extracted from the same locations identified in the first stage of analysis and compared across groups using SPSS 22, with $p < 0.05$, and post-hoc group comparisons evaluated at a Bonferroni corrected threshold of $p < 0.05$.

## 3. Results

All scans were initially evaluated by a clinical neuroradiologist blind to diagnostic status to identify possible clinically relevant abnormalities. None of the scans showed clinically significant abnormalities, although there was evidence of minimal to mild ventricular prominence ($n = 8$) and mild white matter hyperintensity/hypointensity in some participants ($n = 3$).

As evident in Fig. 1, two regions of the cortex showed significant positive correlations between GMV and TSI, even after whole brain correction for multiple comparisons. Table 1 presents the stereotaxic coordinates for the maximally correlated voxels, cluster volumes, and statistics for these two regions. The most strongly correlated of these regions was a cluster within the right fusiform gyrus. As shown in the left scatterplot of Fig. 1, greater TSI accounted for approximately 66% of the variance in the GMV (1st eigenvariate) of this region after controlling for nuisance covariates, including age, gender, and ICV. The second cluster that correlated positively with TSI was located in the posterior vmPFC, primarily within the gyrus rectus and olfactory cortex regions. In this case, TSI accounted for approximately 57% of the variance in GMV of this region (see Fig. 1). There were no regions showing significant negative correlations with TSI.

To examine the association between the GMV and neuropsychological test performance, the extracted cluster values for these two regions were then correlated with VF, DF, and PVT mean reaction time (RT) scores. As shown in Table 2, after controlling for FSIQ and years of education, none of the four VF indices were significantly associated with either TSI or GMV in either of the extracted clusters. On the other hand, DF1 and DF2 were both positively correlated with TSI as well as GMV in the right fusiform gyrus and bilateral vmPFC clusters (see Table 2 for a complete Table of partial correlations). DF3, however, was not significantly correlated with TSI or GMV. On the PVT, faster RT was associated with greater

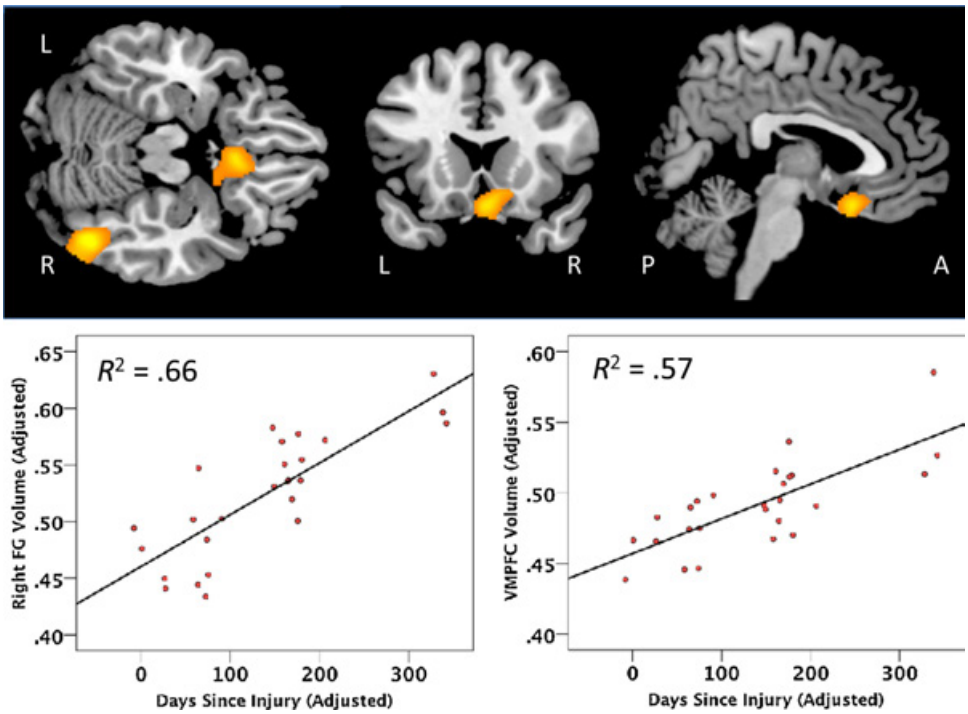


**Fig. 1.** Time since injury (TSI) was positively correlated ($p < .05$, FWE cluster extent corrected) with gray matter volume (GMV) in the right fusiform gyrus (FG) and ventromedial prefrontal cortex (VMPFC; Top Panel; L = left; R = right; A = anterior; P = posterior). The partial correlation scatterplots show the linear association between the adjusted (i.e., residuals re-scaled to raw data) number of days since injury and the adjusted (i.e., residuals re-scaled to raw data) volume of the right fusiform gyrus (bottom left panel) and the ventromedial prefrontal cortex (bottom right panel).

**Table 1**
Cortical voxel clusters significant positive volume correlations with time since injury.

| Target region | Cluster size | MNI coordinates | | | Pearson | |
|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | *r* | *T* |
| Right FG (BA 37) | 1766 | 46 | −61 | −17 | .817 | 6.50 |
| Bilateral vmPFC/GR (BA 25) | 894 | 3 | 18 | −18 | .773 | 5.59 |

All voxels significant at $p < 0.001$ (height) and cluster extent corrected at $p < .05$ (FWE).
BA = brodmann area; FG = fusiform gyrus; GR = gyrus rectus; vmPFC = ventromedial prefrontal cortex.

**Table 2**
Partial correlations (controlling for years of education and full scale intelligence) between time since injury, significant gray matter clusters, and neuropsychological variables.

| Neuropsychological Test | Time Since Injury | Right FG (BA 17) | Bilateral vmPFC/GR (BA 25) |
|---|---|---|---|
| D–KEFS verbal fluency 1 (letter fluency correct) | −0.175 | −0.199 | −0.101 |
| D–KEFS verbal fluency 2 (category fluency correct) | −0.057 | −0.299 | −0.164 |
| D–KEFS verbal fluency 3 (switching correct) | 0.141 | −0.134 | −0.256 |
| D–KEFS verbal fluency 3 (switching accuracy) | 0.094 | −0.160 | −0.306 |
| D–KEFS design fluency 1 (filled dots correct) | 0.443* | 0.422* | 0.417* |
| D–KEFS design fluency 2 (empty dots correct) | 0.415* | 0.358* | 0.418* |
| D–KEFS design fluency 3 (switching correct) | −0.064 | −0.087 | 0.175 |
| PVT mean RT | −0.278 | −0.359* | −0.273 |
| PAI ARD | −0.481* | −0.325 | −0.406* |

*$p < 0.05$ (1-tailed). BA = brodmann area; FG = fusiform gyrus; GR = gyrus rectus; vmPFC = ventromedial prefrontal cortex; D–KEFS = Delis–Kaplan Executive Function System; PVT = 10-minute psychomotor vigilance test; RT = reaction time; PAI = personality assessment inventory; ARD = anxiety related disorders scale

GMV of the right fusiform gyrus, but not with TSI or vmPFC volume. Finally, there was a significant reduction in anxiety symptoms in association with longer TSI and larger GMV within the vmPFC.

Finally, to determine if the increase in GMV reflected a divergence from normal levels, we compared the post-acute, chronic, and healthy control groups using a one-way ANOVA in SPM12. As evident in Fig. 2 Fig., there was a significant effect of group for both the previously identified fusiform gyrus region, $F(2,32) = 72.93$, $p < 0.000001$, and the vmPFC region, $F(2,32) = 39.61$, $p < .000001$. Bonferroni corrected post-hoc comparisons showed that for the fusiform gyrus, GMV differed significantly ($p < .05$) for all three groups, with the chronic group greater than the healthy controls, which were in turn greater than the post-acute group. For the vmPFC, the chronic group showed greater GMV than both the

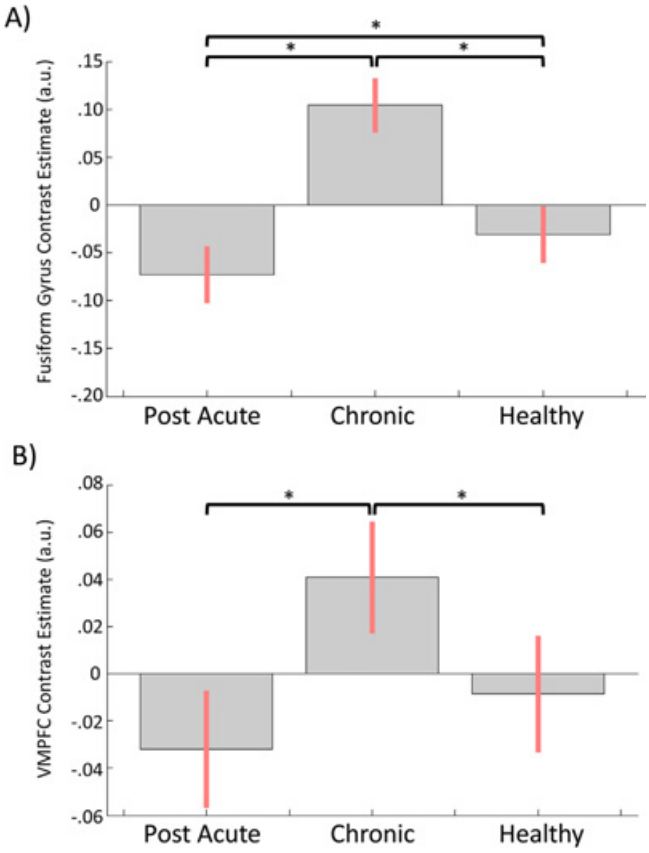


**Fig. 2.** A comparison of mTBI participants in the post-acute (0 to 99 days post injury) or chronic (100–367 days) stage versus healthy controls showed that the chronic stage group had higher gray matter volume within the (A) fusiform gyrus [$x = 46, y = -61, z = -17$] and (B) ventromedial prefrontal cortex (vmPFC) [$x = 3, y = 18, z = -18$] compared to the other groups. Error bars reflect 90% confidence interval. *Comparison is significant at $p < .05$ (Bonferonni corrected).

healthy and post-acute groups, which did not differ from each other.

## 4. Discussion

Several key findings emerged from this study. First, longer TSI was associated with better visual attention, visuo-motor speed, and emotional functioning. Consistent with prior evidence [23], these findings suggest that individuals improve in some visuospatially-mediated neurocognitive abilities and emotional functioning with a longer time window following an mTBI. Moreover, consistent with our hypothesis, we found that greater TSI was associated with larger GMV within the prefrontal cortex, specifically the posterior vmPFC, and also within a region that was not hypothesized—the right fusiform gyrus. Moreover, those with the longest TSI showed increased GMV in these regions that was significantly greater than that observed in healthy controls, suggesting potential focal volume increases beyond normal. Extracted GMV estimates from both of the aforementioned regions correlated positively with several neurocognitive abilities, including visual attention, visuo-motor speed, and nonverbal creativity, suggesting that larger cortical volume of these regions was associated with better visuospatially mediated neurocognitive performance. Finally, there were also regionally-specific neurocognitive correlations, with greater GMV of the fusiform gyrus associated with greater visual psychomotor vigilance performance, while greater GMV of the vmPFC was associated with reduced anxiety related concerns on a self-report measure of psychopathology. Additionally, neither TSI nor its correlated GMV clusters were associated with any aspect of verbal fluency. Together, these findings are generally consistent with our hypothesis that during the first 12 months of recovery from mTBI there is significant remodeling within regions of the cortex that are involved in visual attention, information processing, psychomotor speed, and emotional regulation, and that these GMV structural changes relate to improved performance.

The present findings are correlational and taken from a cross-sectional sample of participants assessed at a single assessment session, so it is impossible to assert a causal mechanism from these preliminary data. However, the associations between larger regional GMV, longer TSI, and improved functioning are consistent with the hypothesis of cortical remodeling over time due to experience-dependent cortical plasticity [15], and the finding that the increases are significantly greater than normal further bolsters this argument. Common complaints of people with persistent post-concussive syndrome include vague difficulties with attention, fatigue, slowed responsiveness, and mood dysregulation [24,28,30]. Evidence suggests that TBI patients expend greater psychophysiological resources to sustain stable cognitive performance over time, which can lead to excessive fatigue [41]. We speculate that as individuals exert effort to overcome these diffuse neurocognitive and emotional regulation problems, they may consistently engage specific brain systems, such as the vmPFC and fusiform gyrus, to *compensate* for their deficits. Through repeated engagement of these cortical regions over many weeks and months post-injury, there may be increased dendritic arborization and spine density within the most utilized areas of the cortex [16], which may ultimately manifest as greater GMV of these structures and contribute to the improvement of some aspects of cognitive and affective functioning. This interpretation does not imply, however, that the regions of increased GMV would necessarily be related to the locus of injury or the particular networks that were damaged. Brain repair and experience-dependent remodeling are likely to involve very different neuroplastic processes, with the former involving heterogeneous regions that differ from one patient to the next, whereas the latter may involve relatively specific regions that are consistently engaged to compensate for common deficits, such as attention or emotion regulation. We therefore suggest that the changes in GMV over time may simply reflect the *compensatory* increase in cortical volume within (potentially non-injured) brain regions that independently contribute to the sustainment of attention, psychomotor speed, and affective regulation, irrespective of the particular location of damage.

The present findings are consistent with evidence suggesting that regular practice of specific motor or cognitive activities can be associated with increased regional GMV [20,32]. For example, recent VBM research with animals suggests that GMV can be increased in a matter of days to weeks in accordance with specific levels of activity or training [25,35]. In humans, similar neuroplastic changes in the cortex have been observed following unilateral eye surgery [20] and even after 12 weeks of self-regulation therapy [32], suggesting use-dependent plasticity. Numerous quasi-experimental and correlational studies show a similar pattern of cortical remodeling with experience. For example, compared to those with less experience, well-trained professional musicians [31], academic mathematicians [1], long-term meditators [18], and people with strong emotional conflict resolution skills [8] exhibit correspondingly larger GMV in specific task-relevant regions, consistent with the hypothesis of experience-dependent plasticity. Our data are consistent with the notion that this process may also play a role during recovery from mTBI.

Our primary hypothesis focused on the prefrontal cortex, because this region is central to most aspects of self-regulation,

including sustaining vigilant attention [13], behavior [7], and emotional control [10], all of which are commonly impaired in patients with mTBI [17,21]. Interestingly, TSI was only associated with larger volume of the posterior vmPFC and not other regions of the prefrontal cortex. The vmPFC has been shown to be particularly important for emotional processing and regulation [37], and GMV of this region was directly associated with lower anxiety related clinical complaints in the present sample. However, this region has not been directly associated with psychomotor vigilance or visuo-motor speed, suggesting that the neurocognitive findings observed here may be related to greater vmPFC mediated self-regulation of anxiety or other aspect of emotional control, which secondarily yielded improved performance on these processing speed-related cognitive tasks.

While not hypothesized, we also found that a cluster within the right fusiform gyrus was significantly larger with greater TSI and correlated with visuo-motor speed and sustained visual psychomotor vigilance. Among the chronic mTBI participants, this region significantly exceeded the volume of normal healthy controls. Recent evidence suggests that the fusiform gyrus plays an important role in protecting cognition from emotional distraction [40]. While speculative, it is therefore possible that this region may show adaptive plasticity to reduce the impairing effects of emotional distraction or frustration that often occur among individuals with persistent post-concussive symptoms. Hence, larger GMV of this region may be associated with greater performance on tasks requiring sustained focus and vigilance. However, as this region was not hypothesized a priori, this possibility remains speculative.

## 5. Conclusion

Among individuals with an mTBI in the preceding year, longer TSI was associated with larger GMV within the vmPFC and right fusiform gyrus. Among those whose injuries were more than three months old, these volumes exceeded those of healthy controls. Functionally, we found that larger GMV of the vmPFC was associated with greater visuo-motor performance and reduced symptoms of anxiety. Larger GMV of the fusiform gyrus was similarly associated with greater visuo-motor speed, creativity, and sustained visual psychomotor vigilance performance. These findings corroborate existing research on compensatory brain mechanisms following mTBI by suggesting that as time elapses following an mTBI, there may be greater compensatory remodeling of distinct cortical regions and particularly those involved in emotional regulation, which in turn may reduce attentional distractibility during timed visuo-motor tasks.

## Conflicts of interests

None declared.

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PERSPECTIVE

# Time dependent differences in gray matter volume post mild traumatic brain injury

When the brain is subjected to excessive physical forces, including blunt impact, high-speed rotation, or blast overpressure waves, its tissue structure and function can be compromised, leading to traumatic brain injury (TBI). Based on the level of structural and functional damage, these injuries can be classified as mild, moderate, or severe, with mild TBI (mTBI) being by far the most common. Also known as concussion, mTBI frequently occurs in a wide variety of activities, including accidental falls, sports injuries, moving vehicle accidents, military training, and combat related events such as blast exposure. mTBI can lead to various cognitive, sensory and motor complaints like reduced memory, attention, and information processing speed, and emotional dysregulation (Carroll et al., 2004). Most individuals with mTBI will recover from these symptoms within 90 days post injury (Karr et al., 2014), but for some individuals, the symptoms may be protracted, persisting up to a year or longer (Satz et al., 1999). For a small minority of individuals, these cognitive and emotional symptoms are severe enough to significantly affect social and occupational functioning.

In contrast to moderate and severe injuries, one of the defining features of an mTBI is the absence of detectible structural lesions on a standard clinical imaging scan. While individual lesions may not be present, there is emerging evidence that, as a group, patients with mTBI may actually be differentiated from non-injured controls based on brain volume data. For instance, previous studies have shown decreased gray matter volume (GMV) post mTBI, suggesting a loss of cortical neurons (List et al., 2015). Very few studies, however, have explored differences in GMV at different time intervals post mTBI and their relationship with neuropsychological performance. Such research is crucial to understanding the recovery process because the brain is not static and neuroplastic remodeling may continue for some time after an injury. Understanding this relationship can facilitate better-targeted intervention strategies to aid in rehabilitation following mTBI.

We recently reported findings suggesting that mTBI may not simply be associated with reduced cortical volume, but instead may show specific increases in gray matter volume (GMV) as well (Killgore et al., 2016). In that project we studied the cortical volume changes and their association with neuropsychological task performance at various time intervals up to a year following injury. We used a 3.0 Tesla magnetic resonance imaging scanner (Siemens Trim Trio, Erlangen, Germany) with a 32-channel head coil for our study. A T1 weighted 3D MPRAGE sequence (TR/TE/flip angle = 2.1 s, 2.3 ms, 12°) was used to acquire 176 sagittal slices (256 × 256 matrix) with a 1-mm slice thickness, yielding a voxel size of 1 × 1 × 1 $mm^3$. The VBM8 toolbox in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used to process the T-1 weighted structural images. All images were spatially realigned to the anterior-posterior commissure axis and then segmented into GM, WM, and CSF using VBM8. A custom DARTEL template was created using the segmented images and then the images were normalized to Montreal Neurological institute (MNI) space. Images were then smoothed with a 10 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

The study participants included 26 right-handed adults (age range 20–45 years, mean age 23.38 ± 5.23, 11 males, 15 females), with English as their primary language. All participants had a history of sports-related mTBI experienced within the 12 months prior to participation this study (2 weeks [$n$ = 2], 1 month [$n$ = 6], 3 months [$n$ = 5], 6 months [$n$ = 10], 1 year [$n$ = 3]). All of these participants sustained mTBI while engaging in sports activities such as rugby ($n$ = 7), basketball ($n$ = 3), softball ($n$ = 1), ultimate frisbee ($n$ = 1), soccer ($n$ = 1), ice hockey ($n$ = 2), lacrosse ($n$ = 1), martial arts ($n$ = 2), weight lifting/gym ($n$ = 4) and track and field ($n$ = 4). The participants were initially screened over the telephone for the details of their head injury, medical and psychiatric history. Participants were ruled out for any serious chronic medical, neurological or psychiatric condition like hypertension, diabetes, epilepsy, bipolar disorder, attention deficit hyperactivity disorder *etc.* The only exception was depression and anxiety developing after the concussion. Also, they were required to provide official documentation of head injury signed by an impartial but professionally responsible witness to the head injury or its immediate consequences (*e.g.*, physician, nurse, ambulance driver, medical records, neuropsychologist). Additionally, 12 healthy control participants (age range 20–43 years, mean age 25.00 ± 6.55, 4 males, 8 females), with no history of head injury or loss of consciousness were recruited as a comparison group. On the day of visit, the healthy and mTBI individuals underwent same series of neuropsychological assessments and MRI sequences.

Remarkably, in contrast to the general finding of reduced GMV following mTBI found in other studies, our results did not show such reductions, but instead showed that longer time since injury (TSI) was associated with increased GMV in two brain regions (see **Figure 1**), including the cortex of the right fusiform gyrus (RFG) and bilateral ventromedial prefrontal cortex (VMPFC). In other words, the cortex of these regions appeared to be larger among those whose injuries were most

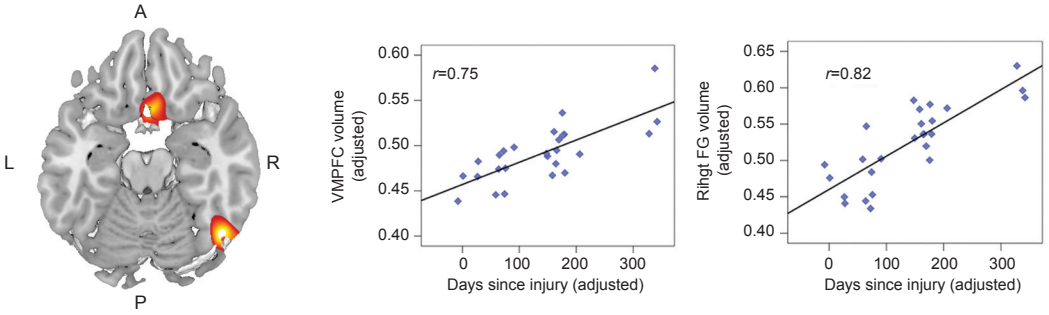


**Figure 1 Regions where larger gray matter volume was significantly correlated with time since injury, including the ventromedial prefrontal cortex and the right fusiform gyrus.**
L: Left; R: right; A: anterior; P: posterior; VMPFC: ventromedial prefrontal cortex; FG: fusiform gyrus.

distal in time. Moreover, larger GMV was associated with better performance for visual motor, visual attention, and emotional functioning tasks, suggesting that greater cortical volume in specific regions was associated with better functional outcome. We speculate that these data point toward significant cortical remodeling occurring in the months following injury. To further evaluate that possibility, we divided our sample roughly in half so that we could compare those in the post-acute stage (0–99 days post-injury) to those in the chronic stage (100–365 days post-injury), and further compared them to a separate sample of healthy individuals with no reported history of head injury. Consistent with our hypothesis, the chronic group showed significantly greater GMV in both regions compared to the post-acute group, confirming that gray matter was increased with longer TSI. Moreover, the chronic group also showed significantly greater GMV compared to the healthy controls, suggesting that not only was the GMV returning to normal with greater TSI, it was actually exceeding the volume seen in healthy normals. Thus, for these individuals, the later stages of recovery were associated with exaggerated GMV in specific regions that are involved in regulating emotion as well as sustaining visual attention and information processing speed.

We interpreted these findings as evidence of experience dependent cortical plasticity. In other words, we propose that for many individuals, mTBI leads to a host of subtle core cognitive impairments and emotional regulation deficits post-injury, which over time, lead the injured individual to draw upon these other cortical regions to compensate. For example, reduced frustration tolerance and emotional dysregulation are common experiences after mTBI and are not specific to a particular lesion site (Ryan and Warden, 2003). It is conceivable that individuals with these emotional difficulties may more routinely activate the ventromedial prefrontal cortical regions, which play an important role in emotional and visceromotor regulation, in an attempt to maintain emotional control. Similarly, many people experience slowed processing speed and attentional difficulties following a concussion (Levin et al., 1987). This may cause such individuals to draw more heavily upon regions such as the fusiform gyrus and other visual attention regions in order to compensate. With sustained and exaggerated use, it is conceivable that these highly exercised regions may begin to develop larger cortical volume through more extensive dendritic arborization. It is well established that repeated practice with certain motor or cognitive skills can lead to an increase in specific cortical regions supporting that skill (Quallo et al., 2009). The preliminary findings from our study are encouraging, suggesting that mTBI is not uniformly defined by decreased cortical volumes. On the contrary, regional increases in volume are possible within this population and these volume changes are associated with improved cognitive and emotional functioning. The fact that we identified specific regions of volume increases is remarkable given the fact that mTBI is an extremely heterogeneous injury, with multiple potential causes and diffuse locations of damage (Bigler, 2008). The fact that these areas of increased volume were consistent and focal suggests that they are likely independent of lesion location—rather they likely reflect common pathways for compensation that are relatively independent of the site of impact or location of damage.

Previous studies have shown that behavioral experience interacts with regenerative and degenerative changes in the brain to induce structural and motor plasticity (Kerr et al., 2011). Compensatory remodeling is one of the ways neuroplasticity works and may undergird the mechanisms behind rehabilitative training, which forms one the mainstays of treatment post mTBI. On the basis of our findings we suggest that rehabilitative training might be even more beneficial if it can capitalize on this aspect of neuroplasticity. Perhaps by focusing rehabilitation efforts toward exercising existing compensatory skills that draw upon these regions (*e.g.*, emotional regulation; regulating attention from distraction), patients can further develop the cortical volume of those regions and, over time, gain greater functional capacity. This would be encouraging and suggest that there is more that could be done for patients recovering from concussions than merely to "wait and see." Clearly this is speculative at this point, but further research should examine whether the cortical volume, structural and functional connectivity, and functional capacity of these same regions can be voluntarily enhanced in patients recovering from mTBI *via* focused training. Finally, it will be important for future work to focus efforts toward using functional neuroimaging. This will enable linkage among the cognitive tasks and identified deficits caused by an injury and the regions of increased gray matter volume identified in our study.

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CHAPTER

# 3

c0003

# White Matter Abnormalities in MS: Advances in Diffusion Tensor Imaging/Tractography

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OUTLINE



s0010

## A BRIEF OVERVIEW OF THE NEUROPATHOLOGY OF MULTIPLE SCLEROSIS

p0045 Multiple sclerosis (MS) is an acquired progressive inflammatory demyelinating condition affecting the central nervous system (CNS) that often presents with a relapsing and remitting course. To understand the symptoms and presentation of MS, it is crucial to first understand the basic neuropathology and associated neuroanatomy that is affected by the disease. MS generally involves neuropathology affecting three primary features of the neuron and surrounding tissue. These features are lesions, inflammation, and damage to the myelin sheath that surrounds the axons of a neuron. As shown in Fig. 3.1, a neuron is composed of cell body with branch-like dendrites and a longer fiber projection called an axon. It is the axons that permit neural communication over significant distances within the nervous system. A neural signal originating in the cell body travels along the axon and terminates at the synaptic bouton, where neurotransmitters are released into the synapse to stimulate adjacent neurons. The terms gray matter (GM) and white matter (WM) are often used to describe various aspects of these neuronal tissues. Specifically, brain tissue such as the cerebral cortex is often labeled as GM because it comprises dense clustering of the cell bodies of neurons, leading to a characteristic grayish appearance to the naked eye or when seen on standard T1 magnetic resonance imaging (MRI) scans. WM comprises the axons and their surrounding myelin insulation. The axon is a protoplasmic projection from the cell body that allows rapid transduction of an electrochemical signal, known as an action potential, across longer distances of the nervous system. In humans, axons are insulated by a fatty white-appearing covering called myelin. The layer of myelin is produced by the attachment of glial cells to the axon (oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system, PNS). The myelin sheath covering is discontinuous and the gaps between the myelin sheath on axon are known as nodes of Ranvier. These gaps allow exchange of ions with the extracellular space which helps regeneration of action potential across the axon. The myelin covering enables faster conduction

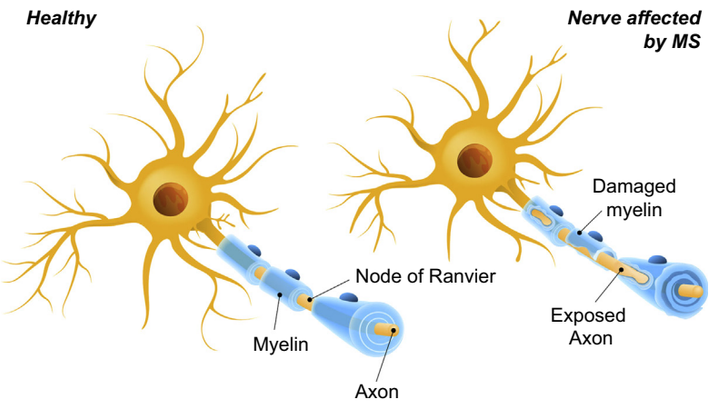


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**FIGURE 3.1** A graphical representation of the anatomical structure of a neuron and comparison between a healthy neuron and a neuron affected by multiple sclerosis (MS). As shown in the figure, the myelin sheath surrounding the axon is damaged in MS. *Reprinted with permission from* www.123rf.com*; designua © 123RF.com.*

[AU10]

of the action potential across neurons by permitting the neural impulse to propagate rapidly from node to node.

p0050 In brief, the pathology of MS involves damage to the myelin sheath, which results in disturbances in conduction of nerve impulses, which in turn affects motor, sensory, visual, and autonomic systems.[11] These disturbances may manifest in several ways. First, lesions (or plaques) to the WM, brain stem, basal ganglia, optic nerve, and spinal cord are among the most commonly observed.[12] These lesions are a result of demyelination and subsequent attempts of remyelination, which builds up plaques along the damaged axons eventually.[12] MS also is associated with the loss of oligodendrocytes, which are responsible for the production of myelin in the CNS.[12] Second, MS can lead to a disruption of the blood–brain barrier, which allows T cells to enter the CNS and initiate a cascade of other immune responses, which in turn commences inflammation.[12] There are four clinical subtypes of MS[8]: (1) relapsing remitting (RR) type—which is the most common pattern and involves periods of flair-ups followed by periods of relative dormancy; (2) secondary progressive (SP) type—which involves a slow worsening of symptoms over time, often with a relapsing and remitting progression; (3) primary progressive (PP) type—which involves a slow but fairly consistent worsening of symptoms over time, without a clear relapse/remission pattern; and (4) progressive relapsing type—which involves a progressive worsening of symptoms with acute periods of exacerbations without clear remissions.

## NEUROIMAGING IN MS

s0015

p0055 MS is a challenging disease when it comes to diagnosis and treatment. Over the past decade, the development of new imaging modalities such as MRI has revolutionized the management of this disease, particularly with regard to diagnosis and monitoring disease progression. In this chapter, we briefly outline the use of standard clinical MRI scans for diagnosis and monitoring, and introduce the investigational use of newer cutting edge neuroimaging technologies, such as diffusion tensor imaging (DTI) and fiber tractography, which hold the promise of rapidly advancing understanding of this debilitating disease.

p0060 MRI is a widely used imaging modality that provides excellent resolution of the lesions common to MS. Standard MRI scans work on basic principles of quantum mechanics. In brief, during a typical MRI scan, the body part of interest is placed within a strong magnetic field, which aligns a large number of the hydrogen protons in the direction of the magnetic field. By applying a radio frequency (RF) pulse to the body part, the orientation of the protons can be momentarily reoriented. After cessation of the RF pulse, the realignment of the protons with the magnetic field will lead to a change in magnetic flux which can be captured by the receiver coil in the scanner and used to reconstruct three-dimensional images of the body part. Depending on the pulse sequences and imaging parameters used, the MRI can produce various sequences such as T1-weighted (T1WI), T1 contrast-enhanced (T1C), T2-weighted (T2WI), fluid-attenuated inversion recovery (FLAIR), DTI, and magnetic resonance spectroscopy (MRS), each providing meaningful information about the health and structure of the tissues and structures being imaged. Fig. 3.2 shows examples of T2WI scans showing MS lesions. MRI scans can be used clinically to make a diagnosis of MS. The McDonald criteria,[13] currently considered the most reliable method of MS diagnosis, rely upon MRI to demonstrate the dissemination of lesions in time and space. Table 3.1 represents the most recent (2011) version of these criteria for using T2WI MRI images to diagnose MS.[18] In the next

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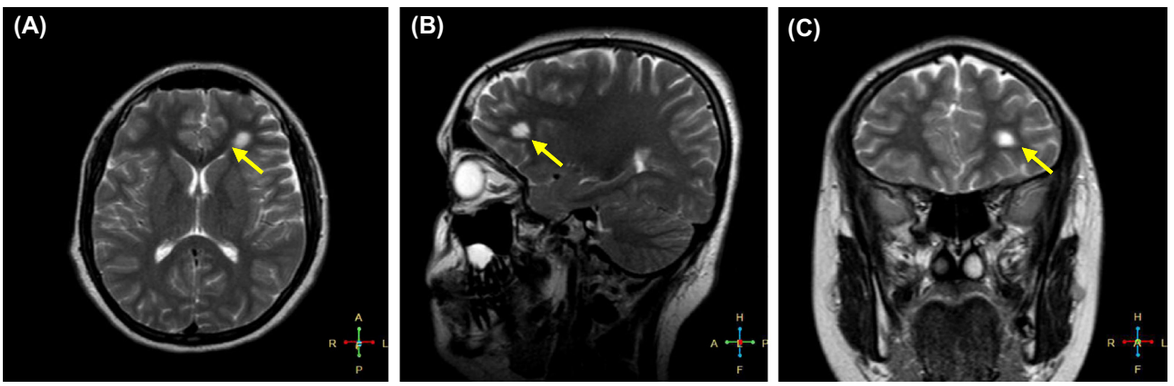


**FIGURE 3.2** T2 weighted structural scans showing an oval shaped hyperintense lesion in the left forceps minor region on (A) axial view, (B) sagittal view, and (C) coronal view. *Reprinted with permission from* www.radiopaedia.org*; image courtesy of Dr. Ahmed Abd Rabou.*

t0010 **TABLE 3.1** Revised McDonald Criteria[18]

| Dissemination in Space | Dissemination in Time |
|---|---|
| ≥1 T2 lesions in two or more of the following locations:<br>• Periventricular<br>• Juxtacortical<br>• Infratentorial<br>• Spinal cord<br>  ◦ If a patient has a brain stem/spinal cord syndrome, the symptomatic lesion(s) are excluded from the criteria, not contributing to the lesion count | • A new lesion on follow-up MRI-T2 lesion and/or gadolinium enhancing<br>or<br>• Presence of asymptomatic gadolinium-enhancing lesion and a nonenhancing T2 lesion on any one scan |

[AU5]

few paragraphs, we outline some of the major findings on each type of MRI scan in patients with MS.

s0020 ## T1-Weighted Imaging

p0065 While T1WI provide exquisite detail of the brain and show clear demarcation between GW and WM, they are not as sensitive as T2WI for detecting MS. In general, T1WI findings vary on the basis of duration and severity of the disease. Axonal loss or destruction in early stages of disease can appear as hypointense or isointense ovoid, rounded or linear shaped lesions, appearing as dark spots on the scan. These are usually seen along the callososeptal interface or periventricular area and are referred to as T1 *black holes*. Sometimes, as the disease progresses the black holes may be marked by a peripheral rim of hyperintensity due to macrophage infiltration and lipid peroxidation of the surrounding tissues. This gives the lesions a *beveled* or a *lesion-within-lesion appearance*. In advanced stages of disease, thinning of corpus callosum (CC) with or without generalized brain atrophy can be seen on T1WI.

s0025 ## T1-Weighted Contrast Imaging

p0070 Adding a contrast agent to an MRI scan can help in identifying certain lesions or pathologies. In the case of MS, gadolinium contrast can be used with a T1 sequence to highlight the actively demyelinating lesions. The lesions can appear punctate, nodular, or rim shaped contrast-enhancing lesions in the cerebral WM. An incomplete rim with the open nonenhancing end facing toward the cortex resembling a horseshoe is a characteristic finding of MS seen on this sequence. The "horse shoe sign" represents active stage of disease. Treatment with steroids drastically suppresses the enhancement and appearance of these lesions.

## T2-Weighted Imaging and FLAIR

s0030

p0075 The T2 sequence, especially FLAIR, is considered to be the most sensitive MRI scan for detecting MS plaques. These images are helpful for identifying lesions because they suppress the appearance of cerebrospinal fluid, which allows for greater resolution in detecting lesions in the periventricular regions. Multiple hyperintense lesions, sometimes surrounded by hypointense peripheral rim with perilesional edema, can be seen. The lesions can be ovoid (as shown in Fig. 3.2), linear, circular, or triangular in shape. A triangular shaped lesion with the base of triangle adjacent to the lateral ventricle and apex pointing toward the cortex is one of the typical findings of MS. Perivenular collection of inflammatory cells along medullary veins can be seen as hyperintensities

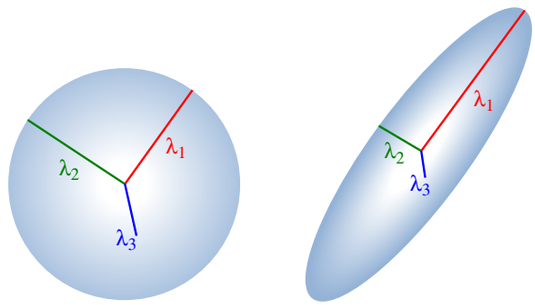


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**FIGURE 3.3** Illustrative example of prototypical water diffusion. Isotropic diffusion means that water molecules can diffuse equally in all directions, as illustrated by a spherical pattern. Anisotropic diffusion means that water molecules are constrained and diffuse more readily in one direction ($l_1$) than in the other two directions ($l_2$ and $l_3$).

perpendicular to the lateral ventricles on axial and sagittal views. This finding is referred to as *Dawson fingers*. The callososeptal interface may show alternate areas of hyperintensity and hypointensity on FLAIR sagittal view giving a dot–dash appearance. This is known as the *dot–dash sign* and is one of the earliest characteristic finding of MS.

## s0035 Magnetic Resonance Spectroscopic Imaging

p0080 Proton MRS is one of the unique applications of the MRI technique. It yields the information about the chemical composition of different metabolites in the tissues rather than information about anatomical structure or function. Biochemical changes are common within a tissue that is affected by certain disease states. These changes are then compared with the normal distribution of the chemicals to assess the degree and extent of damage within that tissue. While the range of neurochemicals that can be assessed with MRS is limited, there are some that may be particularly important in the case of MS. In particular, N-acetyl aspartate (NAA) is an extremely abundant chemical in the brain, particularly within myelin, so it could be an indicator of WM damage in MS. In fact, evidence reported in 2014 supports the suggestion that in primary and SP type of MS the MRS shows decreased levels of NAA, suggesting a biomarker of axonal damage.[27] Other neurochemicals have been found to be elevated in acute lesions of MS, including the levels of myoinositol, choline, and glutamate.[25]

## s0040 Diffusion Tensor Imaging

p0085 DTI is a relatively new neuroimaging technique that has been used to study WM alterations in a great variety of conditions, ranging from depression, to traumatic brain injury, to MS. DTI measures the movement of water molecules within the living tissue,[2] permitting inference regarding the underlying structure of the tissues and their membranes. The motion of water molecules can be described in geometric terms as either resembling a sphere or an elongated ellipsoid and is characterized as being either isotropic or anisotropic in nature, respectively. Isotropic movement occurs when water molecules are unconstrained and free to move in any direction equally, and would thus be best defined as a spherical diffusion pattern. On the other hand, water moving in a tube or garden hose would move preferentially in one direction much more than in other directions, and would therefore be better characterized as anisotropic (i.e., an ellipsoid) pattern of diffusion.[2] For instance, due to the lack of axons within the brain ventricles that would have restricted the movement otherwise, the water is free to move in any direction and hence the movement within these structures would be described as being isotropic. In the brain WM, on the other hand, the presence of axons restricts the movement of water molecules in a particular direction and therefore movement within WM regions is predominantly anisotropic in nature.

p0090 Axons are not always perfectly aligned along one axis and in order to avoid having to measure diffusion along an impractically large number of axes, a concept of diffusion ellipsoid has been developed.[15] The diffusion ellipsoid is defined using three eigenvectors that have three corresponding eigenvalues ($\lambda_1$, $\lambda_2$, and $\lambda_3$) that describe their physical length.[16] The longest, medium, and shortest eigenvectors are represented by $\lambda_1$, $\lambda_2$, and $\lambda_3$, respectively.[16] Fig. 3.3 shows the relationships between these three eigenvectors for isotropic and anisotropic shapes.

p0095 A number of diffusion measurements have been developed in an attempt to characterize diffusion patterns within the brain WM. Fractional anisotropy (FA) is a global diffusivity measure that measures the degree of anisotropy and is used to evaluate WM integrity. FA is defined by the following formula[15]:

$$FA = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

p0100 FA values range from 0 to 1, with higher values indicating higher anisotropy (i.e., water diffuses more along one axis relative to the others). Mean diffusivity (MD) has also frequently been used to measure the overall diffusivity and represents the average of the three eigenvalues[29]:

$$MD = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3}$$

p0105 Two other DTI metrics that have been proposed to further explain changes in the global measures (i.e., FA

and MD) are radial diffusivity (RD) and axonal diffusivity (AD). RD is used to measure diffusion across the axon whereas AD describes movement of water molecules along the axon. Changes within these metrics have been attributed to demyelination and axonal damage, respectively. In their pioneering studies, Song and colleagues showed that loss of myelin following retinal ischemia in mouse optic nerve was associated with increased RD and unchanged axial diffusivity. [22–24] Moreover, they showed that axonal degeneration observed during histological analysis was concurrently associated with reduced AD and unaltered RD.[22] Therefore, these metrics have been used to describe potential reasons for changes within the global diffusivity measures. RD is defined in the following way[23]:

$$\lambda\perp = \frac{(\lambda_2 + \lambda_3)}{2}$$

AD is represented by $\lambda\| = \lambda_1$[23].

## DTI Findings in MS

Using conventional MRI, earlier studies were able to demonstrate macrostructural damage, such as WM lesions, that underlie the physical and cognitive disturbances that are commonly observed in MS. With application of DTI to a wider range of illnesses including MS, both physicians and scientists were able to better understand this condition on a microstructural level. One of the earliest studies by Werring, Clark, Barker, Thompson, and Miller[28] showed reduced FA and high MD in normal-appearing white matter (NAWM) in frontal, parietal, temporal, and occipital regions. Based on the earlier description, this suggests that MS is associated with regions of greater spherically shaped diffusion, potentially suggesting poorer axonal integrity or disruption of myelin (see Fig. 3.4B and C). An important implication from these findings is the notion that WM changes may start occurring before clinical symptoms emerge and remain undetectable using conventional MRI and hence potentially delay clinical interventions that could affect the onset of the illness or reduce its severity.

More recent studies have rectified this earlier limitation by investigating individual WM fiber bundles with the advent of WM tractography (Fig. 3.4A), an outgrowth of DTI procedures. This technique allows a more accurate identification and description of WM architecture. As shown in Fig. 3.4, it is possible to use the FA values at individual locations throughout the brain to determine the probable fiber pathways representing large bundles of axons and plot them for visual representation. Fink et al.[5] have investigated coherence within a number of WM regions including the uncinate fasciculus (UF), superior longitudinal fasciculus, fornix, and cingulum in a group of MS patients. The left UF showed reduced FA and increased MD while the right UF was characterized by increased RD. Increase in RD has been frequently interpreted to signal demyelination.[22] In addition, there was a bilateral reduction in FA within the fornix. Similar to the UF findings, increased RD was observed in the left cingulum.

Similarly, Hecke et al.[7] used voxel-based morphometry that implements whole-brain approach to studying brain WM to examine WM microstructure in RR and SP MS. They have demonstrated reduced FA in a number of WM tracts including the inferior longitudinal fasciculus (ILF), capsula interna, and forceps major in MS patients. There were also changes in AD that were consistent with the FA findings such that lower AD was observed in the ILF and capsula interna, as well as in the body of the CC and corona radiata (CR). Increased MD and RD were observed in the ILF, the capsula interna and externa, genu, body, and splenium of the CC, forceps major, and CR. These findings therefore indicate that MS is characterized by both axonal damage and demyelination, although the precise location of the damage varies by tract.

Kern, Sarcona, Montag, Giesser, and Sicotte[9] studied the relationship between WM integrity and motor function in RR MS using whole-brain DTI analysis as well as probabilistic tractography. This study observed 7.1% decrease in FA in the CC, CR, cingulum, and internal capsule, with concurrent 24.95% increase in RD within these regions, thus suggesting demyelination. Other regions with reduced RD included the cortico-spinal tract, right cerebellar peduncle, right external capsule, and left cerebellum. These changes in WM metrics were related to performance of motor tasks. In particular, reduced FA and increased RD in the body of the CC and mid-posterior CR was associated with reduced right-hand performance on the nine-hole peg test (NHPT). Increased RD in cortical WM adjacent to the left motor and right frontal cortices also predicted poor right-hand performance on the NHPT. Furthermore, worse left-hand performance was related to the reduced FA in the body of the CC and a region of occipital WM. These results suggest that at least motor dysfunction observed in MS is differentially affected by WM compromise due to asymmetry. Finally, increased RD at baseline predicted decrease in performance on the NHPT[9].

In 2015, Asaf, Evan, and Anat[1] studied a large sample of RR MS participants using whole-brain analysis approach in order to examine temporal timeframe of WM degeneration. This study included participants with MS at different stages of the disease duration: less than 1 year (short duration), 1 year (medium duration) and over 1 year (up to 6 years; long duration). Compared to medium disease duration, long disease duration was characterized by diffuse reduction in FA, especially in the body of the CC, by 22%. In the short disease duration

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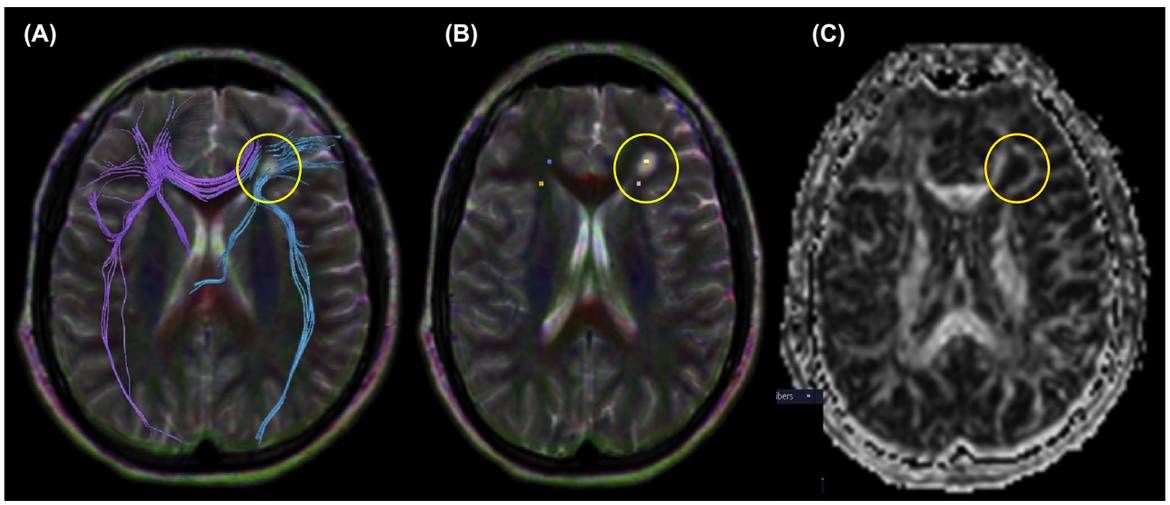


**FIGURE 3.4** DTI findings for a plaque located in the left forceps minor region. (A) A tractographic image revealing destruction of white matter fibers at the site of plaque (*circled*). (B) A combination of anatomical color map with T2WI image with ROI markings at the site of plaque (*circled*) and normal appearing white matter. The circled ROI at the site of plaque shows decreased FA and increase ADC indicating increased diffusion of water molecules. (C) The FA map. White matter fibers appear bright except at the site of the plaque which appears dark as the diffusion becomes isotropic (*circled*). *Reprinted with permission from* www.radiopaedia.org*; image courtesy of Dr. Ahmed Abd Rabou.*

group, FA was reduced by 31% compared to healthy controls, especially in the ILF. There was no difference between the short disease duration and medium disease duration. Overall, disease duration negatively correlated with FA. This study provides evidence for a time-dependent WM atrophy that affects different tracts to a variable degree.

p0140 Similarly, Sigal, Shmuel, Mark, Gil, and Anat[21] showed an association between disease duration and changes in diffusivity measures. Specifically, this study observed a positive correlation between disease duration and rate of relapse and average diffusivity coefficient (ADC). Moreover, lower FA and increased AD and RD were observed in the MS group compared to healthy controls in the whole CC but not within its subregions. These findings further suggest that WM degeneration is temporally contingent. Taken together, these observations led researchers to explore the association between this trend and corresponding cognitive deterioration.

## s0050 Relationship Between DTI Measures and Cognitive Profile of MS

p0145 Following the initial investigations into the WM changes in MS, researchers became interested in examining the effects that these neural changes have on the cognitive profile associated with this condition. Koenig et al.[10] used probabilistic tractography to investigate the relationship between the WM and cognitive function in RR and SP MS. This study observed reduced FA and increased RD, AD, and MD in the posterior cingulate bundle in the MS group compared to controls. The findings also indicated that episodic memory, as measured by the Brief Visuospatial Memory Test-R (BVMT), was a significant predictor of RD in the posterior cingulate bundle. Moreover, speed of processing, as measured by the Symbol Digit Modalities Test (SDMT), was a strong predictor of RD in the posterior limb of the internal capsule and posterior cingulate bundle. Taken together, these findings indicate that MS is associated with WM abnormalities within tracts that have traditionally been implicated in emotion, attention, and memory. These alterations were, in turn, manifested by memory and attention problems.

p0150 Memory problems are frequently observed in MS and have therefore been studied in relation to WM microstructure. Hecke et al.[7] studied working memory in a group of RR MS patients using whole-brain voxel-based morphometry. They observed reduction in FA in the group of MS patients compared to healthy controls in a number of major WM tracts, including the ILF, capsula interna, and forceps major and concurrently reduced AD in the ILF, capsula interna, body of CC, and CR. Additionally, there was an increase in RD and MD in the ILF, capsula interna and externa, genu, body, and splenium of the CC, forceps major, and CR. These diffusion measures were also shown to be related to performance on working memory tasks, such as Paced Auditory Serial Addition Test (PASAT). In particular, there was a significant positive correlation between PASAT and FA in the left ILF, forceps minor, the capsula interna and externa, genu of the CC, left cingulum, superior longitudinal fasciculus (SLF), and CR. This pattern of results was also observed in a study by Syc et al.[26] who used continuous

tractography method to study the microstructure of the cingulum and fornix. This study observed 19% reduction in FA in a group of RR, SP, and PP MS in the fornix, with a concurrent increase in RD, AD, and MD. There was also an increase in RD, AD, and MD within the left and right cingulum, with no significant changes within FA. In the left cingulum, there was a significant association between the diffusivity measures and performance on the PASAT of information processing and attention, where lower scores on the test were associated with lower FA and higher MD and RD.

p0155 Contrary to Syc et al.,[26] using the same tractography method, Ozturk et al.[17] studied microarchitecture of the subregions of the CC in relation to performance on the PASAT in a sample of RR, SP, and PP MS patients. The findings of that study showed reduced FA and increased RD and MD in the whole CC in MS compared to healthy controls. When subregions of the CC were studied individually, a positive correlation was observed between FA and the body and splenium of the CC. This finding not only suggests the involvement of multiple tracts in performance of PASAT but is also indicative of heterogeneous changes within different portions of the CC in this condition. Caligiuri et al.[3] have examined the role of the callosal subregions in cognitive function in MS. They observed an association between FA in the genu and splenium of the CC and cognitive function where cognitive impairment was significantly related to reduction in FA. Since the study by Caligiuri et al.[3] used a compound score to measure cognitive function, it cannot be directly compared to the results of the study by Ozturk et al.[17] who observed change in different subregions of the CC in relation to performance on the PASAT.

p0160 Another test that is frequently used to assess cognitive difficulties observed in MS is California Verbal Learning Test (CVLT), a task specifically designed to assess short- and long-term verbal memory. Performance on this assessment has recently been studied in conjunction with WM damage observed in MS. Using tractography, Fink et al.[5] studied microarchitecture of the UF, SLF, cingulum, and fornix and observed that RD within the UF predicted performance on the encoding subscale of the CVLT. Moreover, this study also showed a significant positive correlation between the recognition subscale of the CVLT and PD in the right fornix. These results indicate that in this clinical population, different aspects of verbal memory are differently affected depending on the specificity of WM damage as assessed by DTI techniques.

### s0055 Relationship Between DTI Measures and Psychiatric Profile of MS

p0165 Apart from the cognitive complaints, emotional problems have also been observed in patients with MS. In particular, depression is one of the most frequently reported psychiatric sequelae. The lifetime prevalence of depression in MS is estimated to be 25–50%.[14] Pujol, Bello, Deus, Marti-Vilalta, and Capdevila[19] studied structural alterations in the frontal and temporal regions in depressed MS patients. Their results showed an association between lesions in the arcuate fasciculus and greater depressive symptoms. These lesions predicted approximately 17% of variance in depressive scores. Feinstein et al.[4] studied NAWM in MS patients. Their results showed greater reduction in FA in the left anterior NAWM in the depressed MS compared to nondepressed MS. Additionally, increased MD was observed in the right inferior frontal lobe.

p0170 In a DTI study reported in 2014, Gobbi et al.[6] performed a whole-brain analysis looking at both PP and SP forms of MS. They observed reduced FA in the forceps minor in the depressed subgroup compared to the nondepressed participants. This finding is of a particular significance given that this region of the CC connects parts of the dorso-medial prefrontal cortex (DMPFC) and has been implicated in the pathogenesis of depression.[6]. Pujol et al.[19] studied the microstructure of the arcuate fasciculus in patients with MS and showed that lesions within this tract were associated with cognitive expression of mood in these patients. After controlling for cognitive deficits, lesions in the arcuate fasciculus predicted 26% of variance in the Beck Depression Inventory (BDI) scores[19] Shen et al.[20] used whole-brain analysis to examine the association between WM architecture and the Hamilton Rating Scale for Depression (HAM-D). This study has showed a positive association between the scores on HAM-D and FA in a number of WM regions including the right precentral gyrus, cingulate gyrus, and posterior cingulate. This is inconsistent with past research showing decreased WM integrity with increased depressive symptoms. This finding may be attributable to the compensatory mechanisms that have been previously observed.

## CONCLUSIONS s0060

p0175 MS is a progressive and debilitating disease that affects the myelin sheath of axonal pathways. Traditional clinical imaging, particularly T2-weighted MRI, has revolutionized the ability of researchers and clinicians to diagnose and track disease progression. These types of MRI scans provide clear evidence of the characteristic lesions of MS. Nonetheless, advances in MRI technology, particularly DTI and fiber tractography are providing even greater resolution and understanding of how MS affects specific fiber tracts and may allow an even more precise monitoring of disease progression. While these

newer DTI methods are still primarily investigational, they hold great promise for furthering understanding of MS and its underlying pathology.

s0065 ## References


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# WATSON: 03

## Non-Print Items

**Abstract**

Multiple sclerosis (MS) is a chronic debilitating disorder affecting the central nervous system (CNS), particularly the white matter. Over the years, there have been significant advances made in the management of MS including diagnosis and treatment. Magnetic resonance imaging (MRI) is one if the neuroimaging modalities which has revolutionized the diagnosis and early detection of the disease. MRI has also proven useful to monitor disease progression in patients with MS and estimate its prognosis. In this chapter we have described the neuroimaging findings in MS using various methods of MRI. On the basis of sequence and imaging parameters applied, MRI scans can provide T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion tensor imaging (DTI), and proton magnetic resonance spectroscopy (MRS) images, all of which may have applicability in the evaluation of patients with MS. Some of these sequences, especially DTI and MRS, have proven particularly helpful in understanding the pathology of this disease from a new perspective. We focus extensively on the recent development and application of DTI and fiber tractography in understanding and characterizing the white matter lesions that occur in MS. The application of these methods holds considerable promise for advancing our understanding of MS.

[AU3]

**Keywords:** Autoimmune; Demyelination; Diffusion tensor imaging (DTI); Diffusion weighted imaging (DWI); Fluid-attenuated inversion recovery (FLAIR); Fractional anisotropy (FA); Magnetic resonance imaging (MRI); Multiple sclerosis; Neuroimaging; Neuron; Tractography.